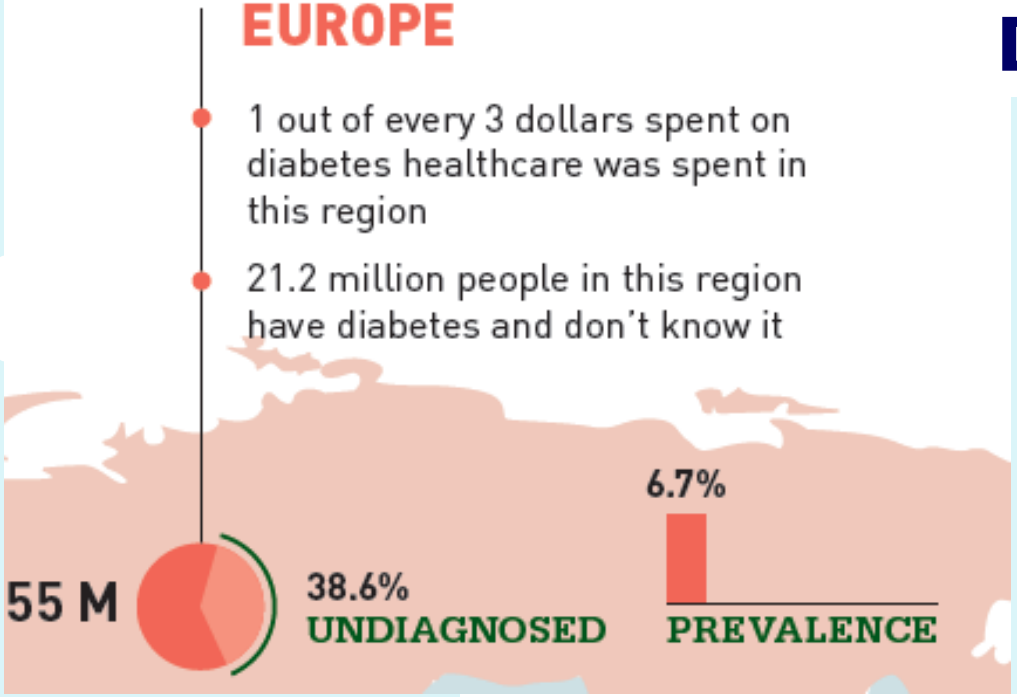
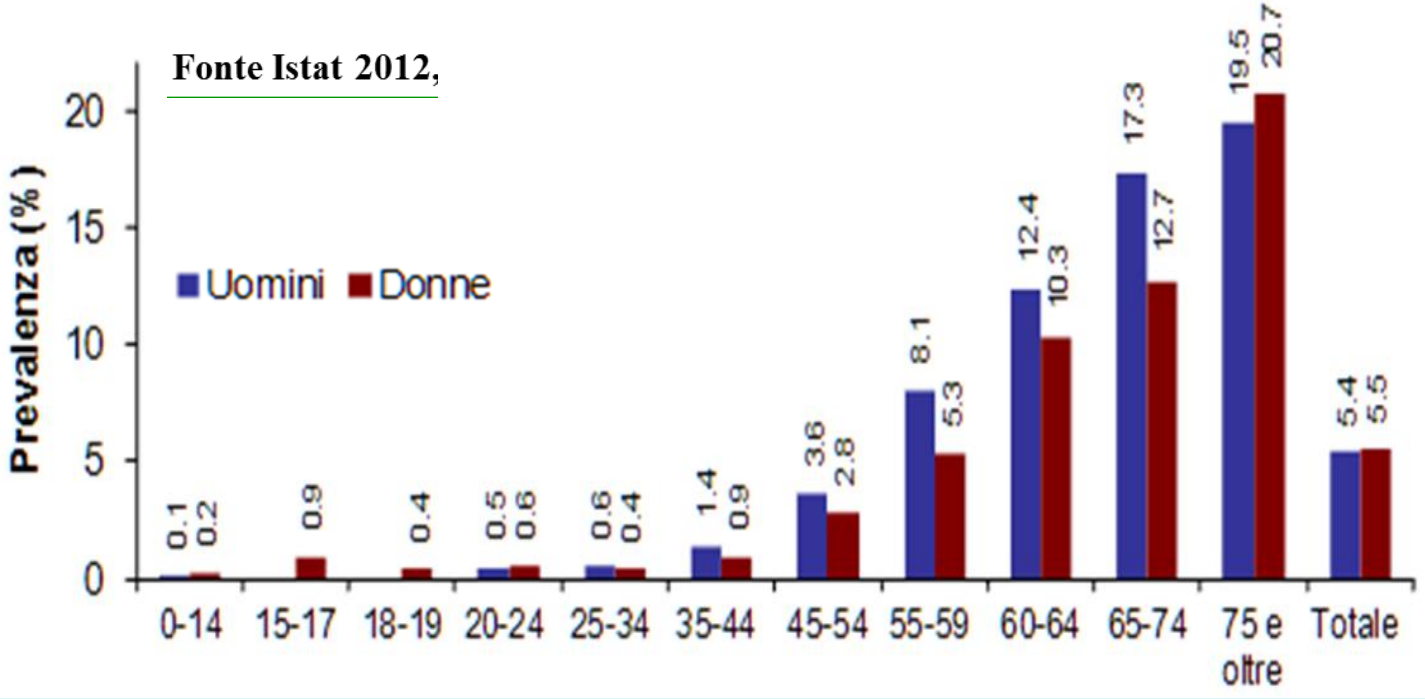
Stroke criptogenico e diabete

Raffaele Marfella

Dipartimento
di Geriatria e Malattie del
Metabolismo
Seconda Università Napoli

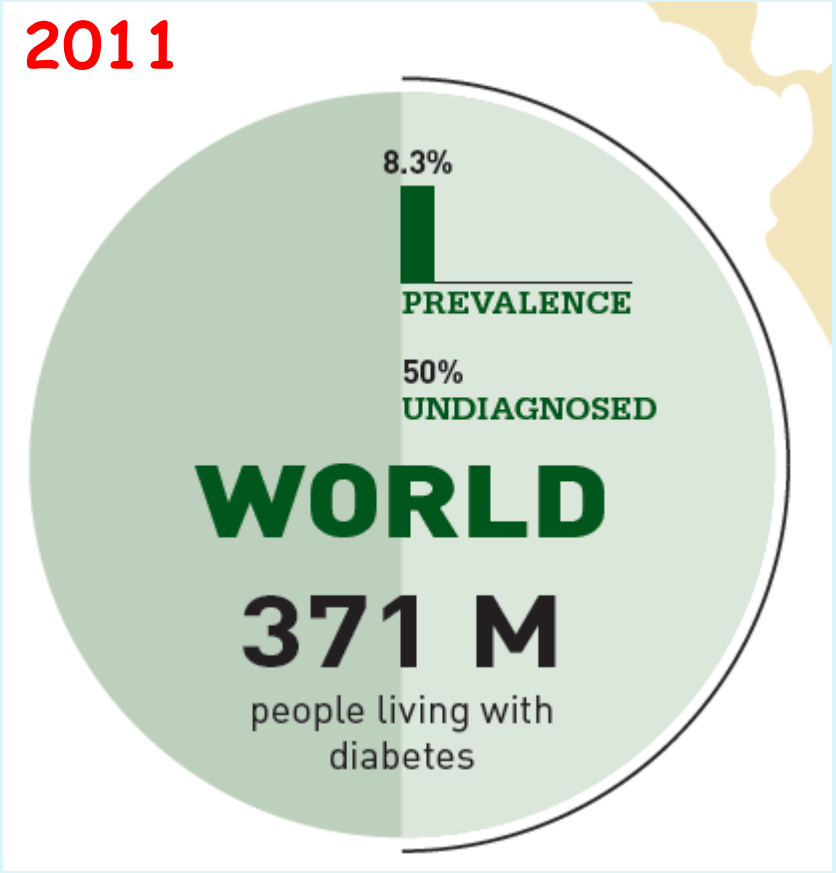
Diabetes Prevalence

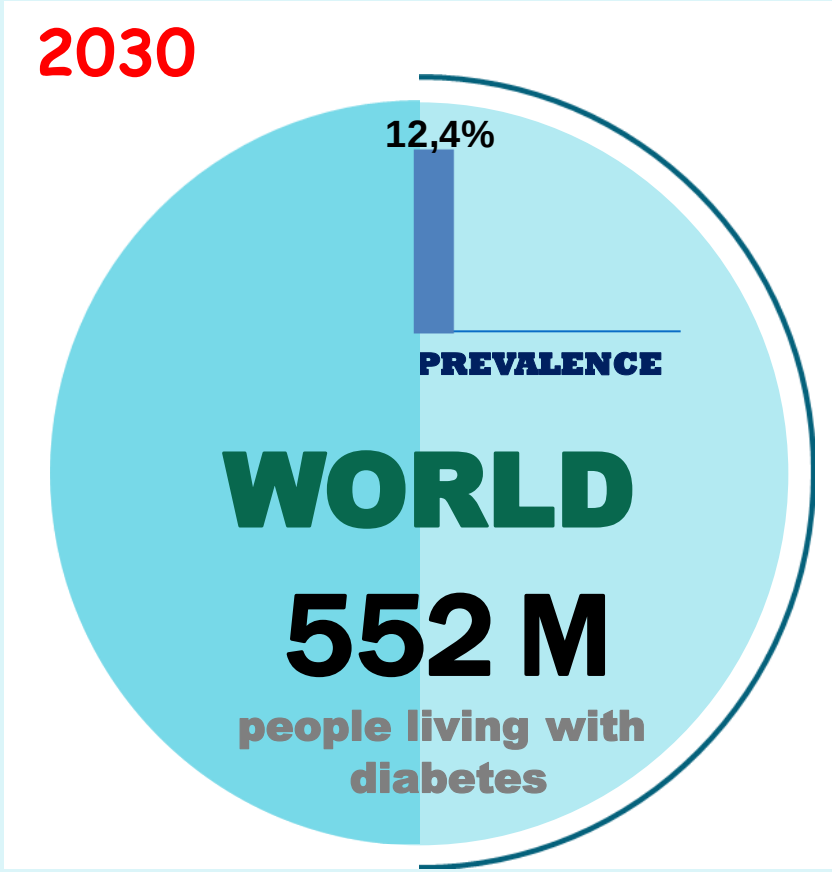




We project that in 20 years the number of people with diagnosed diabetes will increase by 50.7%, from 371 million in 2011 to 552 million in 2030.

The biggest percent increases will be among people aged 65 years (69%)





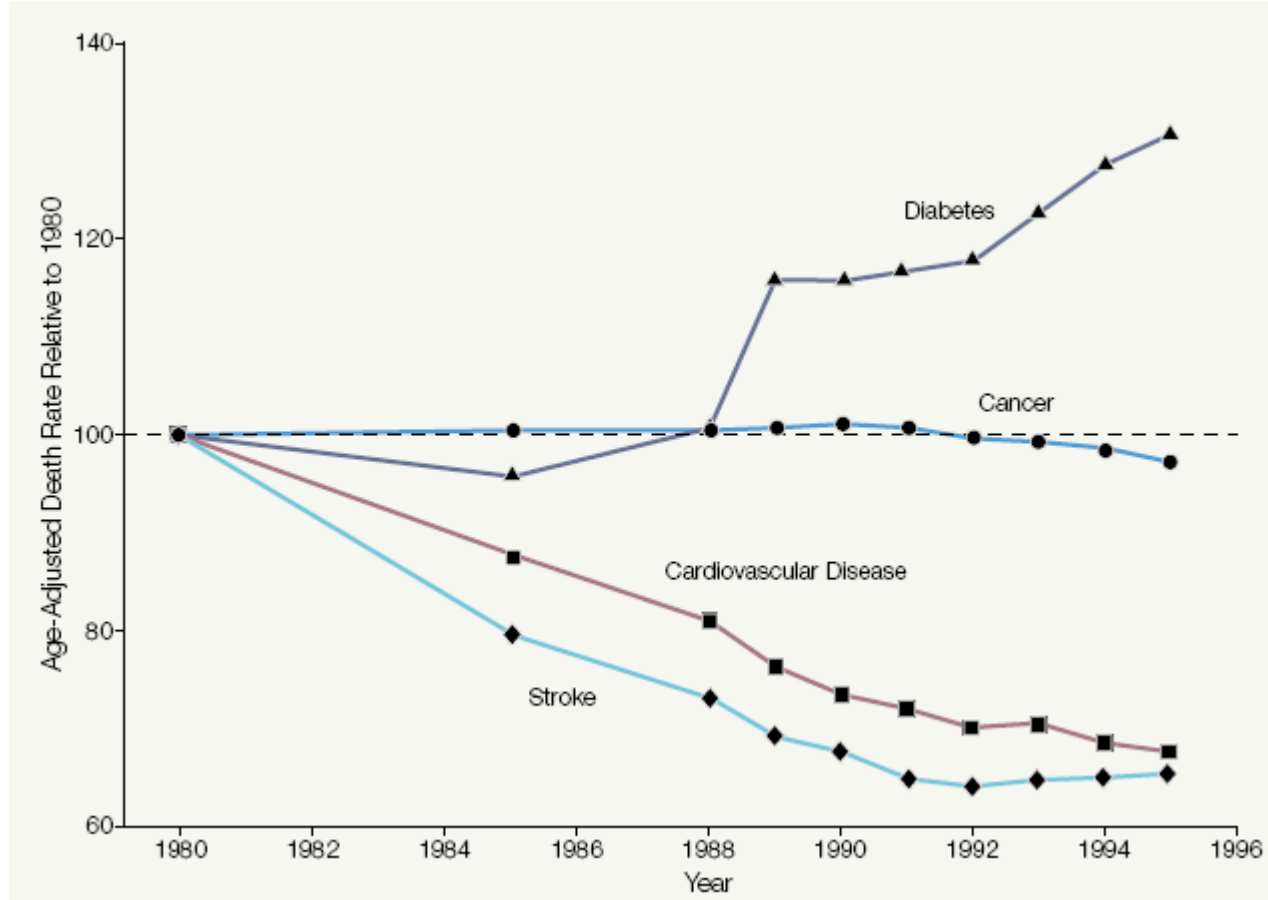
JAMA®
The Journal of the American Medical Association

Prospects for Research in Diabetes Mellitus

Jerrold M. Olefsky, MD

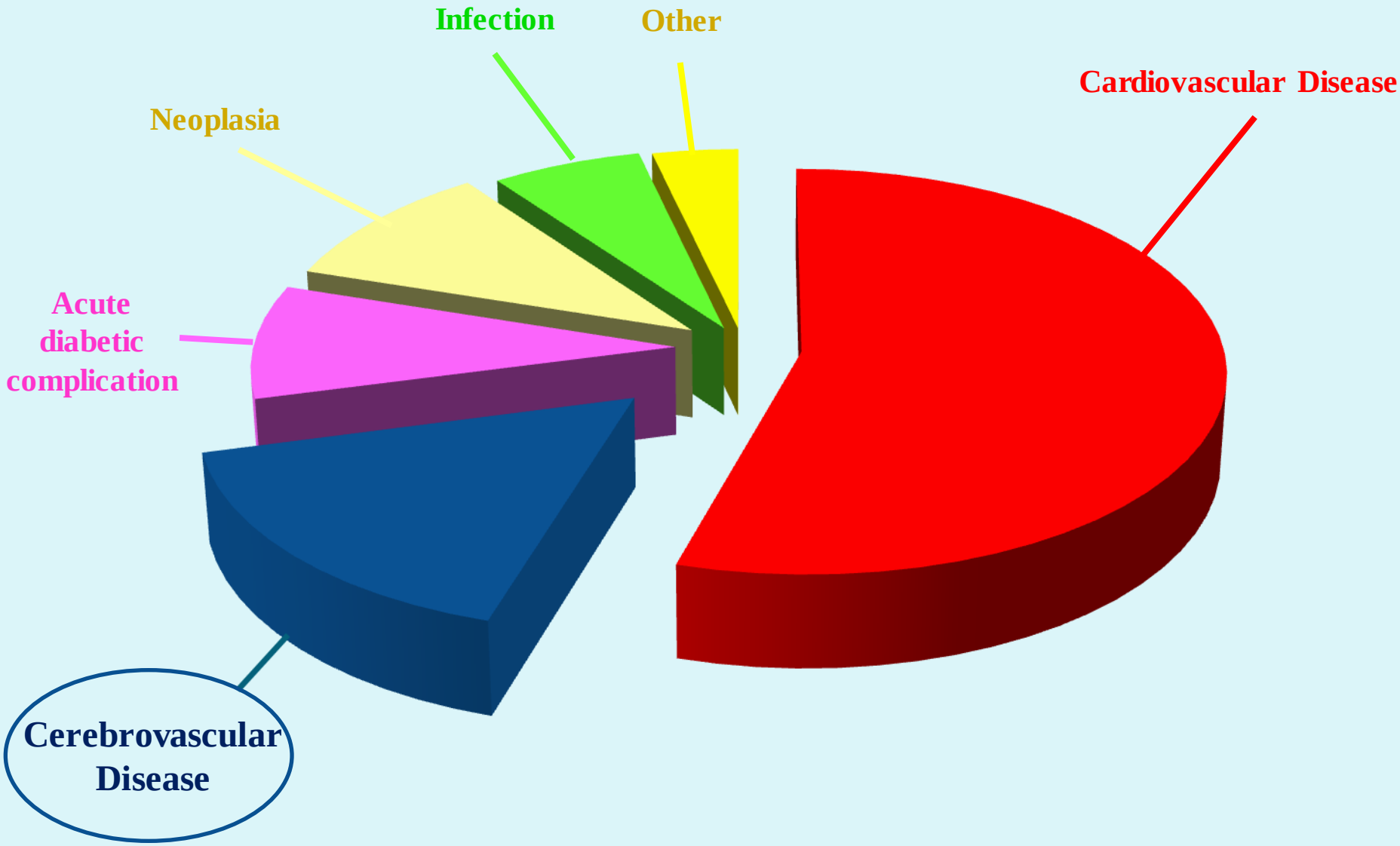
September 13, 2011 (EASD, Lisbon, Portugal)

"This year, 4.6 million deaths will be attributed to diabetes, with 1 person dying from diabetes every 7 seconds."



JAMA, February 7, 2001—Vol 285, No. 5

Etiologies of mortality in patients with diabetes mellitus

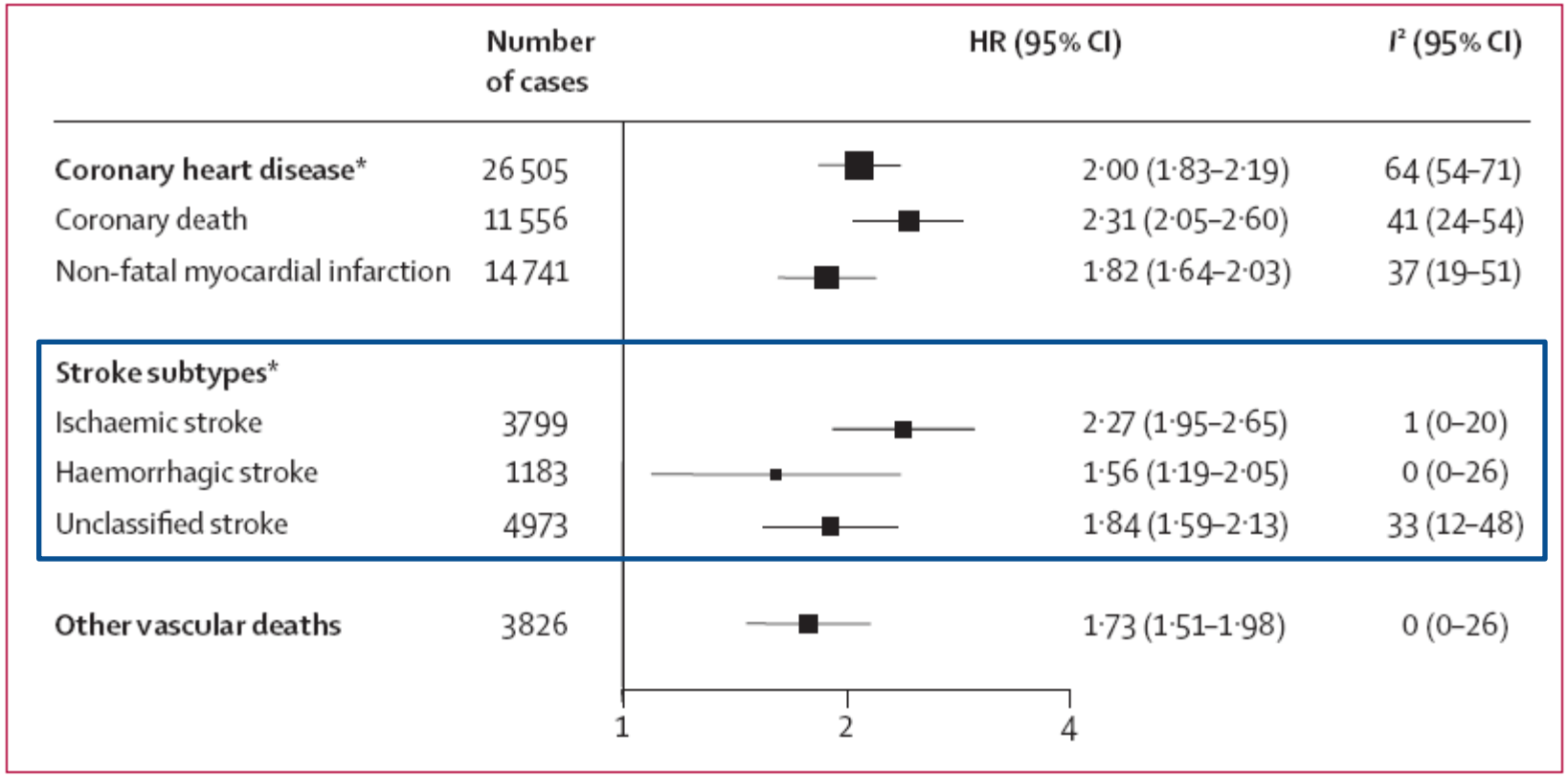


Geiss LS et al. In: Diabetes in America. 2nd ed. 1995;chap 11

Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies

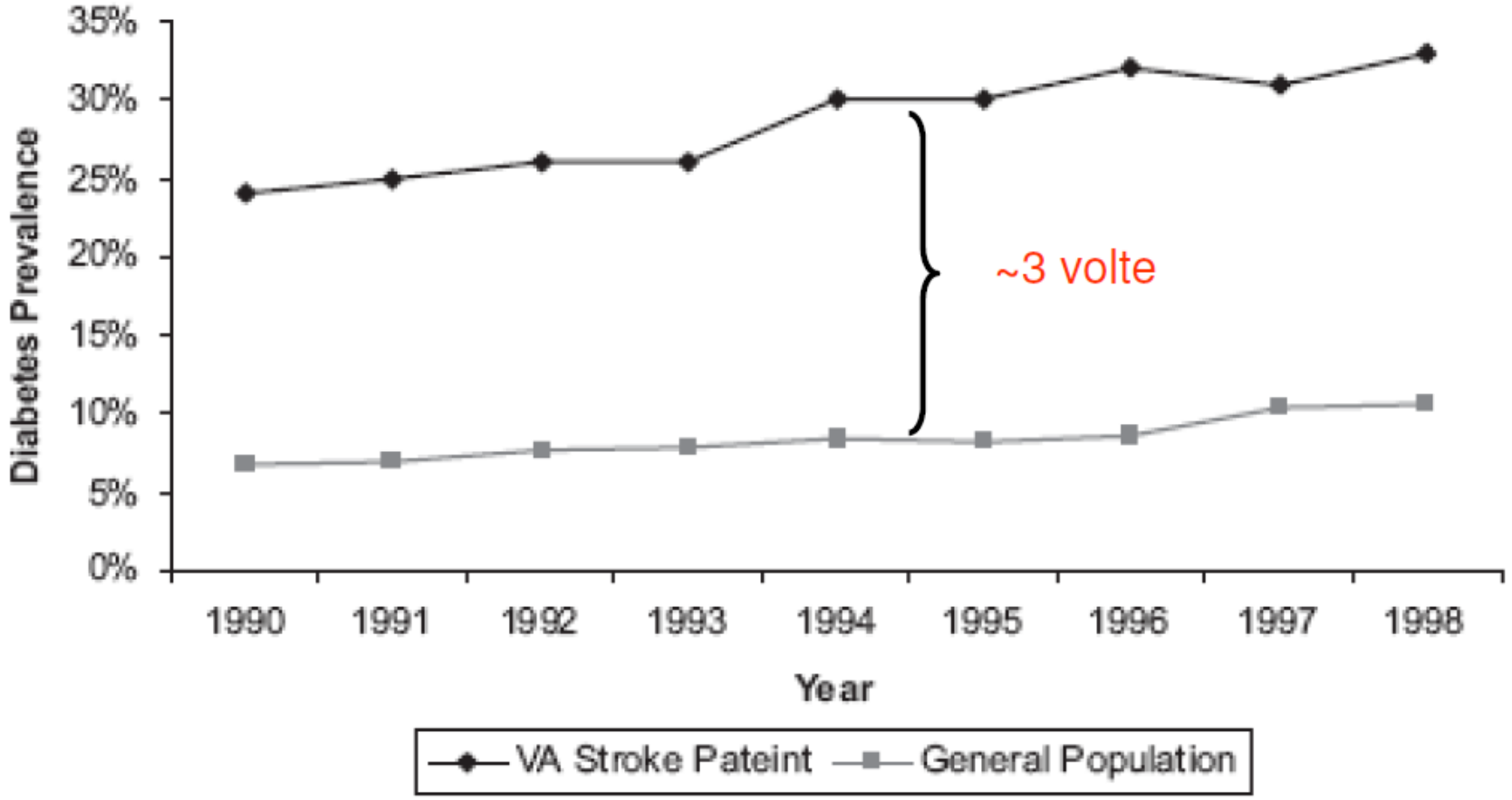
*The Emerging Risk Factors Collaboration**

Analyses included data for 698782 people



Lancet 2010; 375: 2215–22

Diabetes prevalence among stroke patients and general population *(Veterans hospital between October 1990 and September 1997 n=48,733 ischemic stroke patients)*

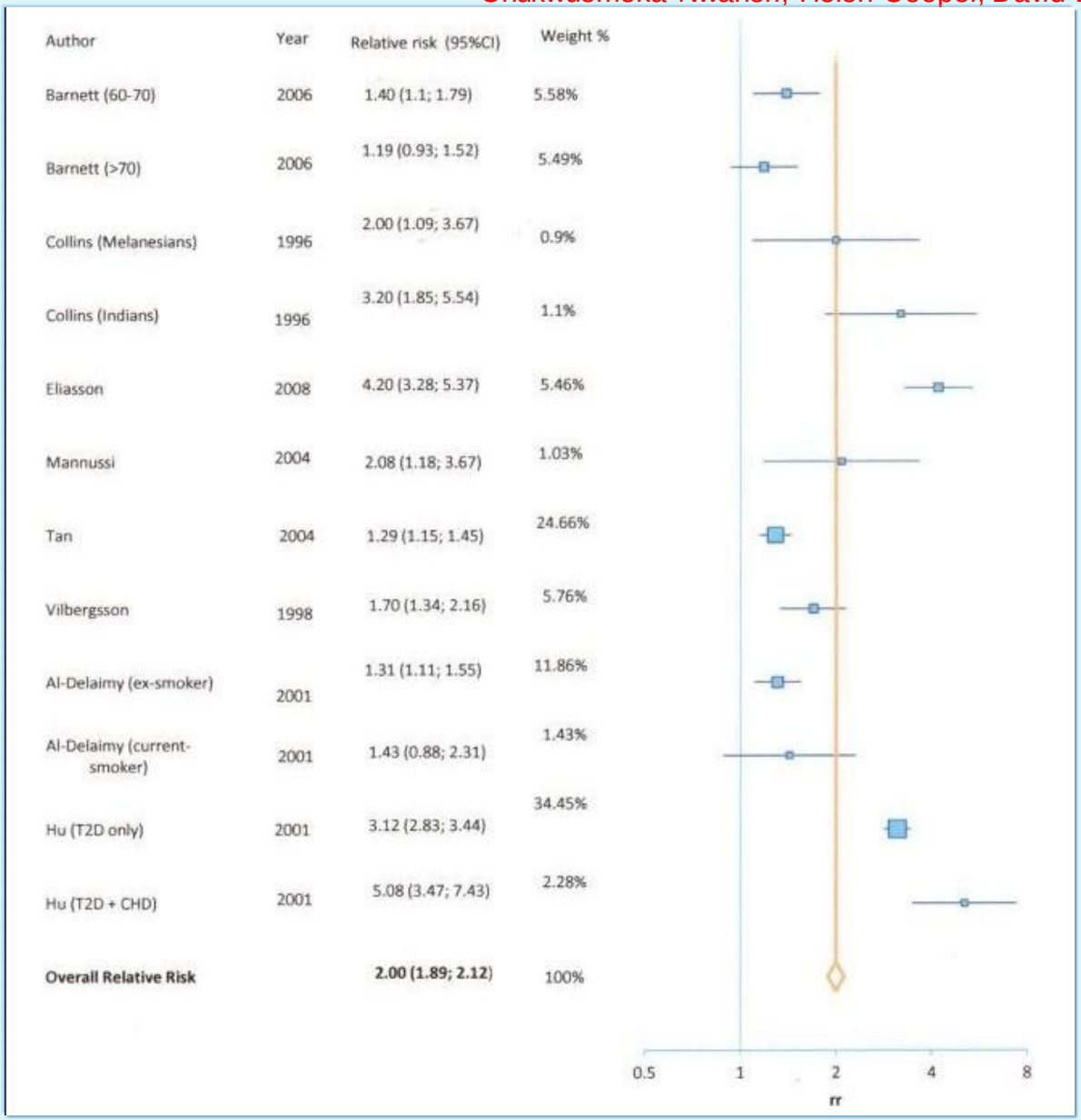


Kamalesh M et al. Stroke. 2008;39:2727-2731

Mortality in Type 2 Diabetes Mellitus

Magnitude of the Evidence From a Systematic Review and Meta-analysis

Chukwuemeka Nwaneri, Helen Cooper, David Bowen-Jones



Relative risks of stroke mortality in type 2 diabetes population.

220,689 patients with a mean follow-up of 10.7 years.

British Journal of Diabetes and Vascular Disease. 2013;13(4):192-207

Epidemiology of stroke in patients with diabetes

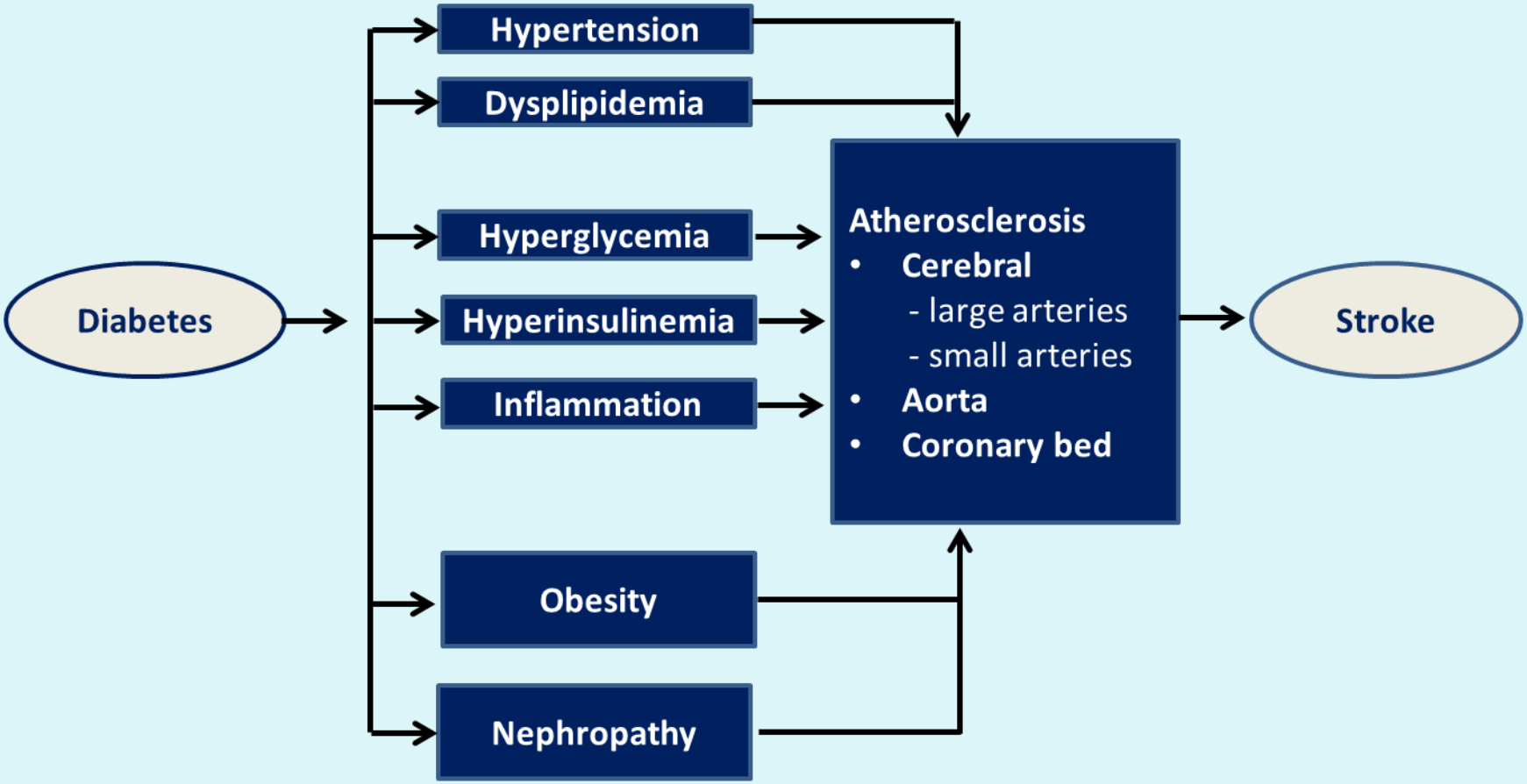
J. Tejada García, L. Redondo Robles

Av Diabetol. 2010;26:397-402

	Diabetes	No-diabetes
Ishemic:hemorrhagic	10:1	5:1
Risk of age <55	Greater	Lesser
RR male/female	Female>Male	Male>Female
Lacunar infarct	More frequent	Less frequent
Silent infarcts	More frequent	Less frequent
Progression of ischemic subcortical lesions	More frequent	Less frequent
Transitory ischemic attack	More recurrence risk	Less recurrence risk
Prognosis	Less favorable evolution in the acute phase More risk of recurrence	

Diabetes and the developement of the stroke

Primary metabolic disturbance → Vascular risk factor → Pathology → Critical event



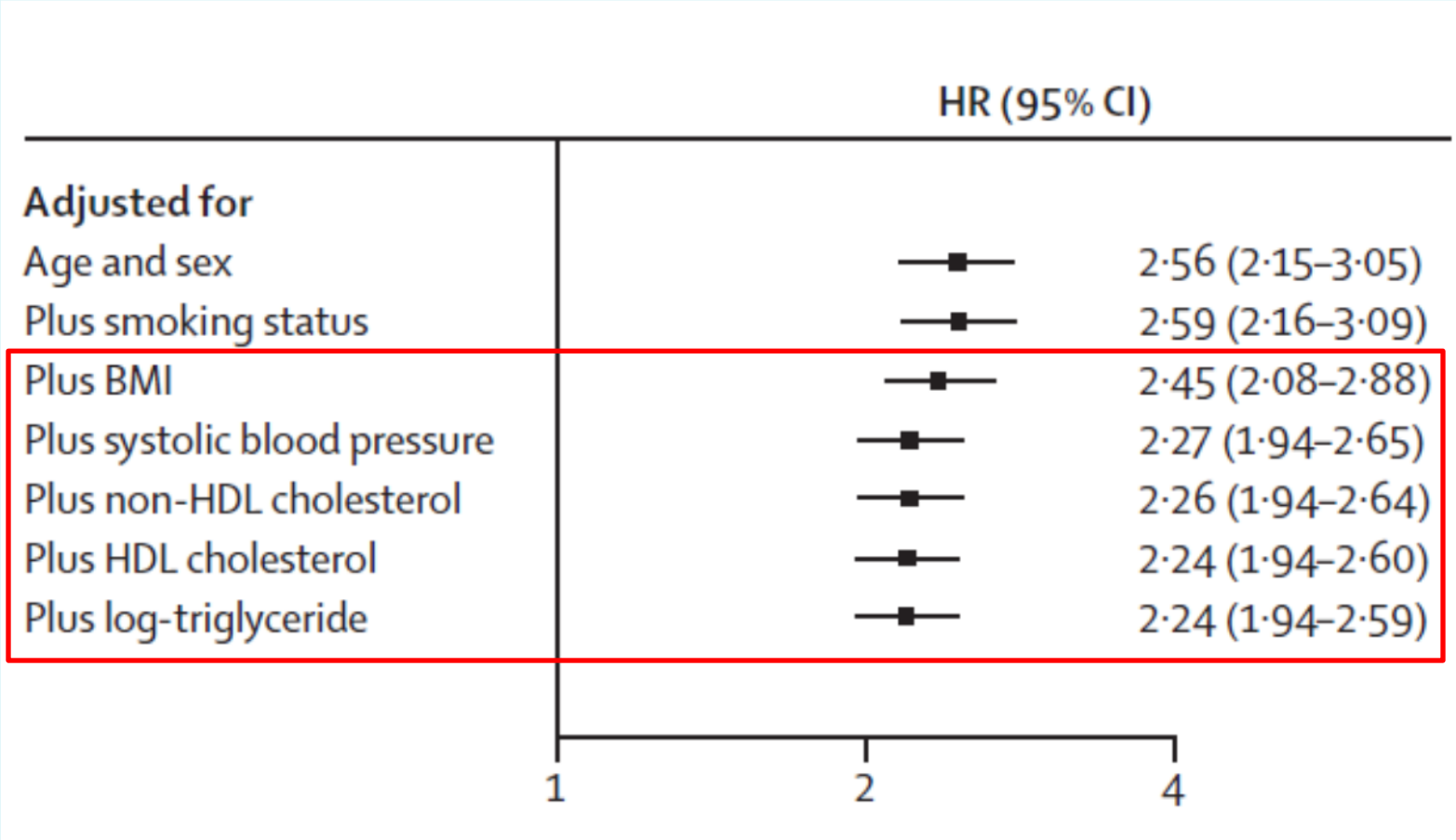
Br J Diabetes Vasc Dis 2008; 8: 222-229

Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies

*The Emerging Risk Factors Collaboration**

Lancet 2010; 375: 2215–22

The risk for ischaemic stroke did not change after additional adjustment for BMI, blood pressure and lipids

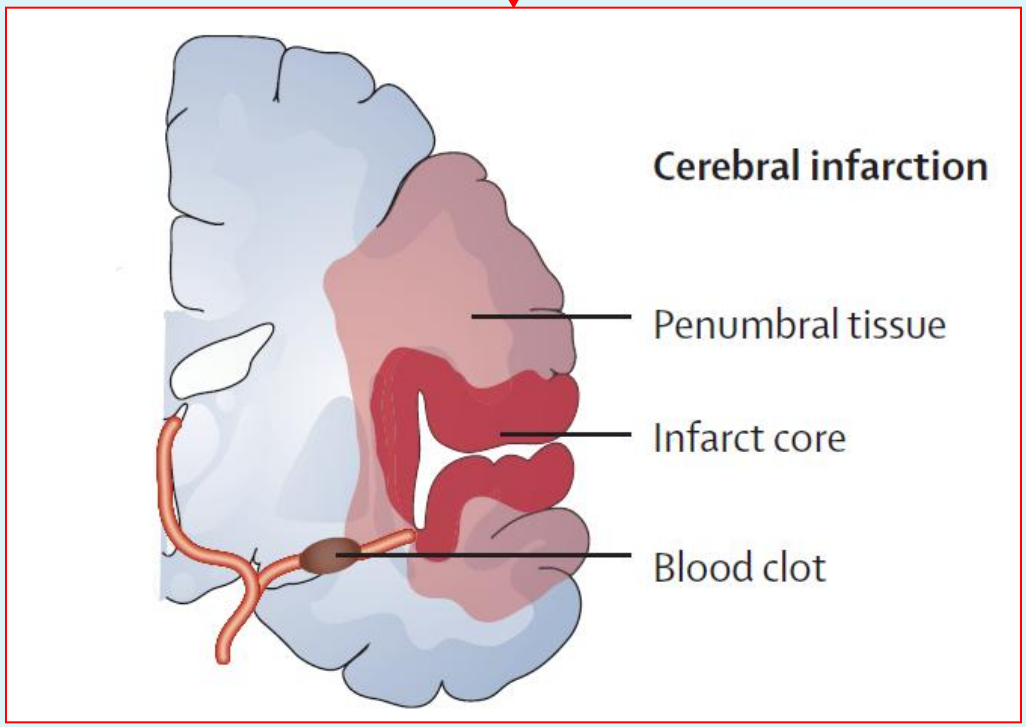


Diabetes, hyperglycaemia, and acute ischaemic stroke

Merel J A Luitse, Geert Jan Biessels, Guy E H M Rutten, L Jaap Kappelle

Approximately one-fourth of strokes in diabetic patients are of unknown cause

Type 2 DIABETES ?



Lancet Neurol 2012; 11: 261–71

Ictus criptogenetico: la fibrillazione atriale alla sbarra degli imputati

Marcella Jorfida, Paolo Cerrato*

Struttura Complessa di Cardiologia a direzione Universitaria, Dipartimento Cardiovascolare Toracico; AUO San G. Battista, Torino
*Stroke Unit, Dipartimento di Neuroscienze; AUO San G. Battista, Torino

Anno V numero III • Giugno 2009

emergency care journal

L'imputato: la fibrillazione atriale asintomatica

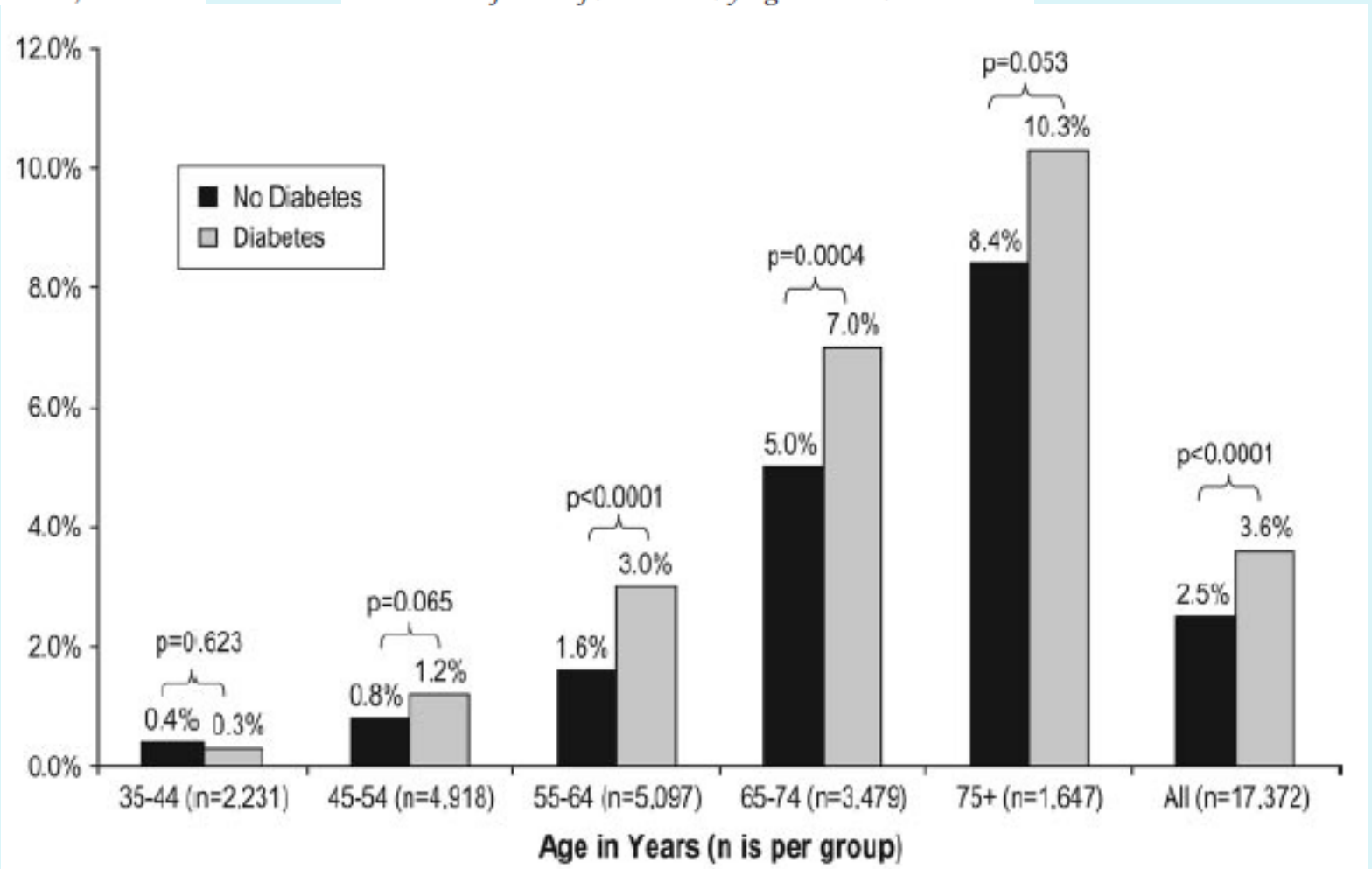
il rischio di un evento ischemico cerebrale sembra essere più frequente dopo la terminazione di una FA parossistica.

Independent Contribution of Diabetes to Increased Prevalence and Incidence of Atrial Fibrillation

GREGORY A. NICHOLS, PHD[1]
KYNDARON REINIER, PHD[2]
SUMEET S. CHUGH, MD[2]

Diabetes Care 32:1851–1856, 2009

Prevalence of atrial fibrillation by age and diabetes status.



Type 2 DIABETES

↓ ?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

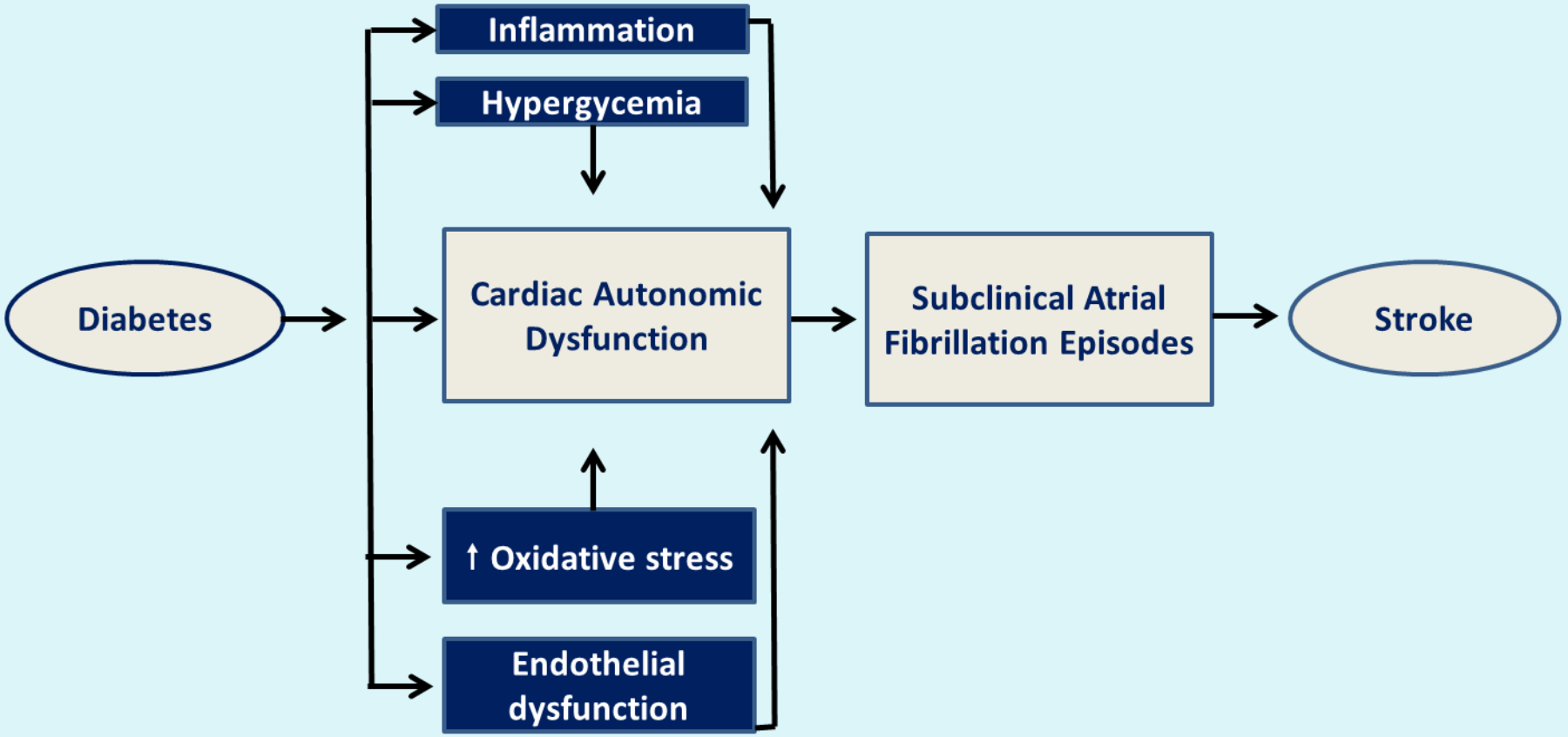
Subclinical Atrial Fibrillation and the Risk of Stroke

Jeff S. Healey, M.D., Stuart J. Connolly, M.D., Michael R. Gold, M.D., Carsten W. Israel, M.D., Isabelle C. Van Gelder, M.D., Alessandro Capucci, M.D., C.P. Lau, M.D., Eric Fain, M.D., Sean Yang, M.Sc., Christophe Bailleul, M.D., Carlos A. Morillo, M.D., Mark Carlson, M.D., Ellison Themeles, M.Sc., Elizabeth S. Kaufman, M.D., and Stefan H. Hohnloser, M.D., for the ASSERT Investigators*

N Engl J Med 2012;366:120-9.

Diabetes and the developement of the cryptogenic stroke

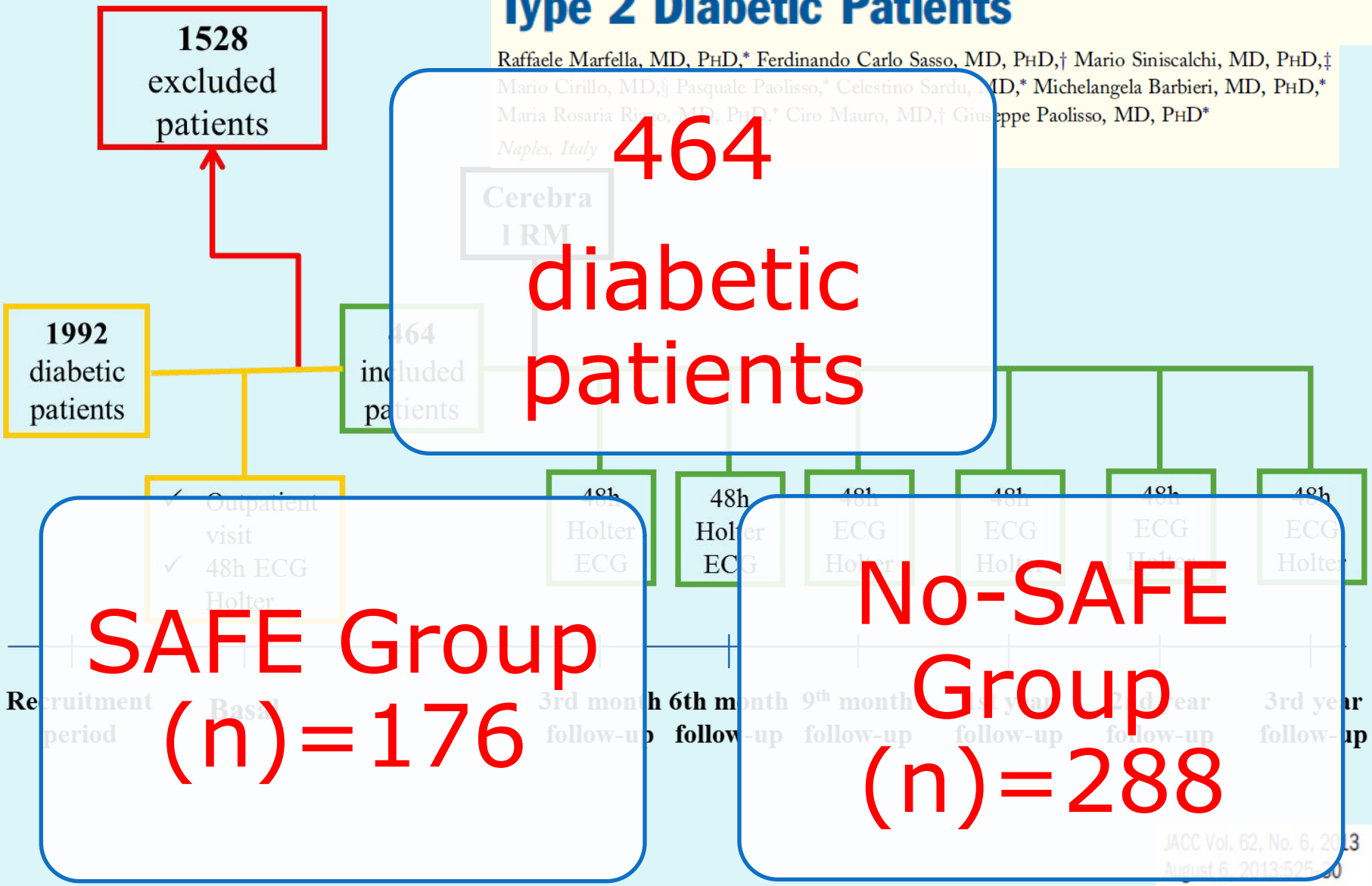
Primary methabolic disturbance → Resulting risk factor → Pathology → Critical event



JACC
Journal of the American College of Cardiology

Brief Episodes of Silent Atrial Fibrillation Predict Clinical Vascular Brain Disease in Type 2 Diabetic Patients

Raffaele Marfella, MD, PhD,* Ferdinando Carlo Sasso, MD, PhD,† Mario Siniscalchi, MD, PhD,‡ Mario Cirillo, MD,§ Pasquale Paolisso,* Celestino Sardu, MD,* Michelangela Barbieri, MD, PhD,* Maria Rosaria Rizzo, MD, PhD,* Ciro Mauro, MD,† Giuseppe Paolisso, MD, PhD*
Naples, Italy



JACC Vol. 62, No. 6, 2013
August 6, 2013:525–30

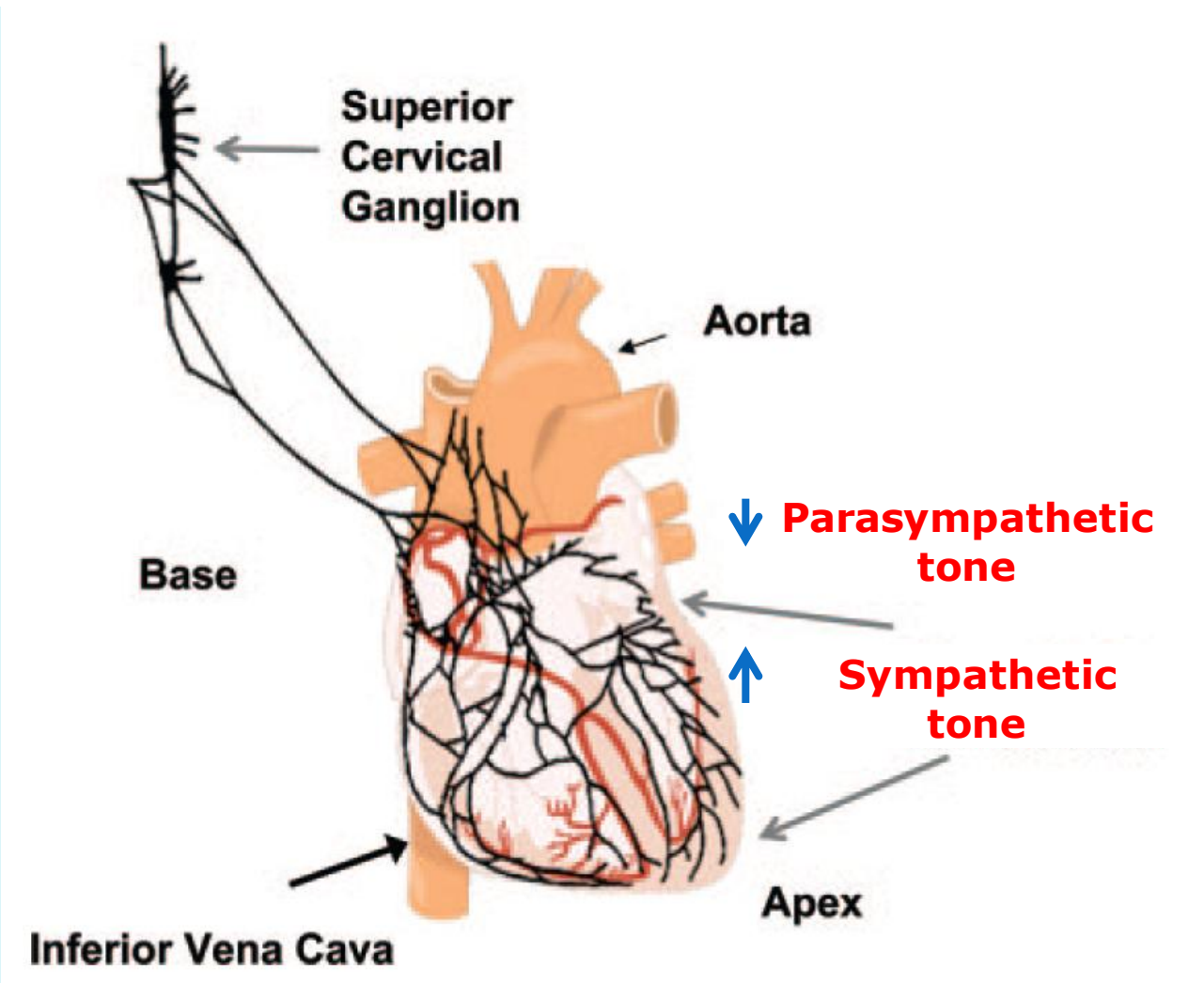
Reviews/Commentaries/ADA Statements
REVIEW ARTICLE

Cardiac Autonomic Neuropathy in Diabetes

A clinical perspective

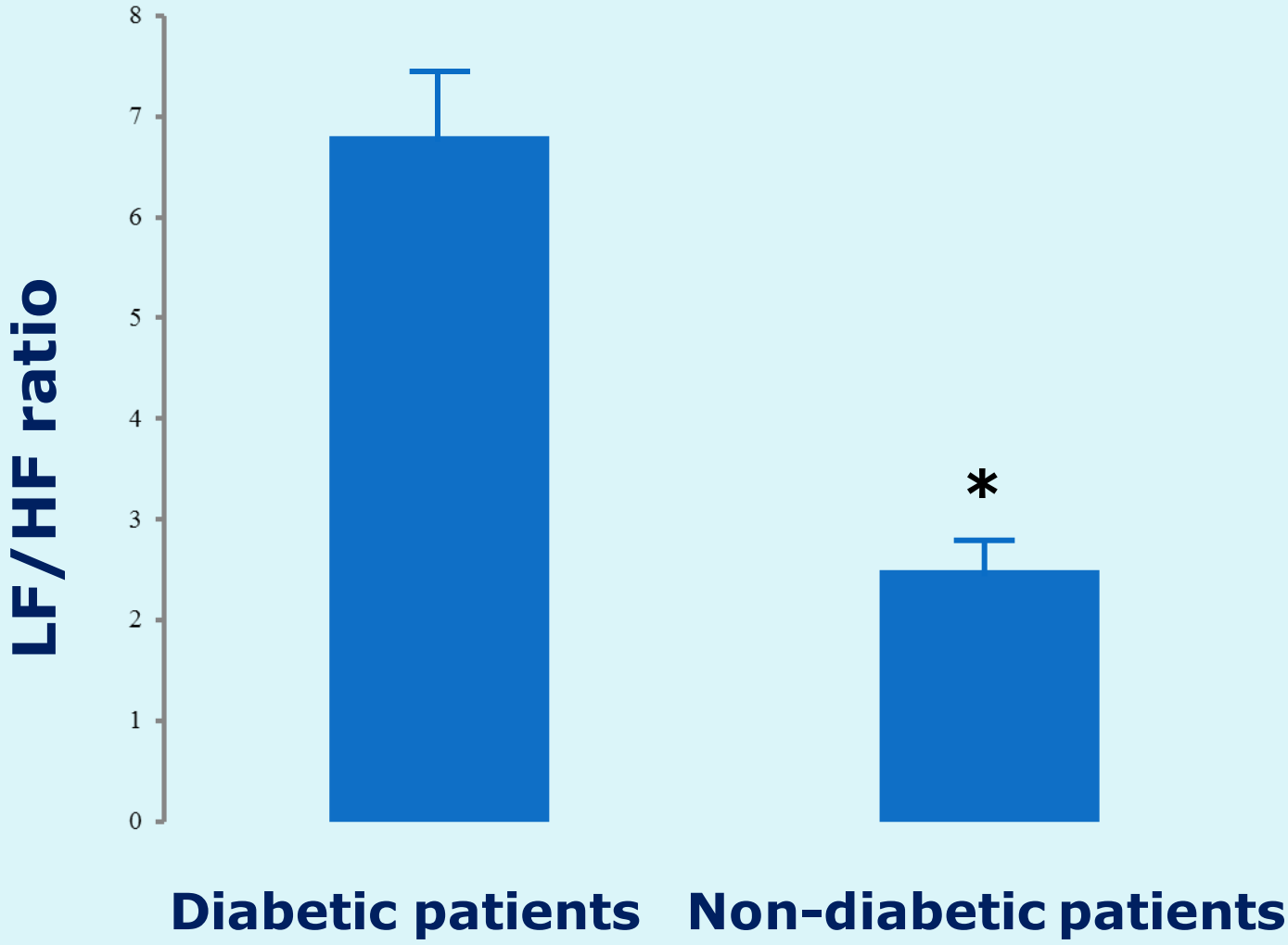
RODICA POP-BUSUI, MD, PHD

DIABETES CARE, VOLUME 33, NUMBER 2, FEBRUARY 2010



HEART RATE VARIABILITY

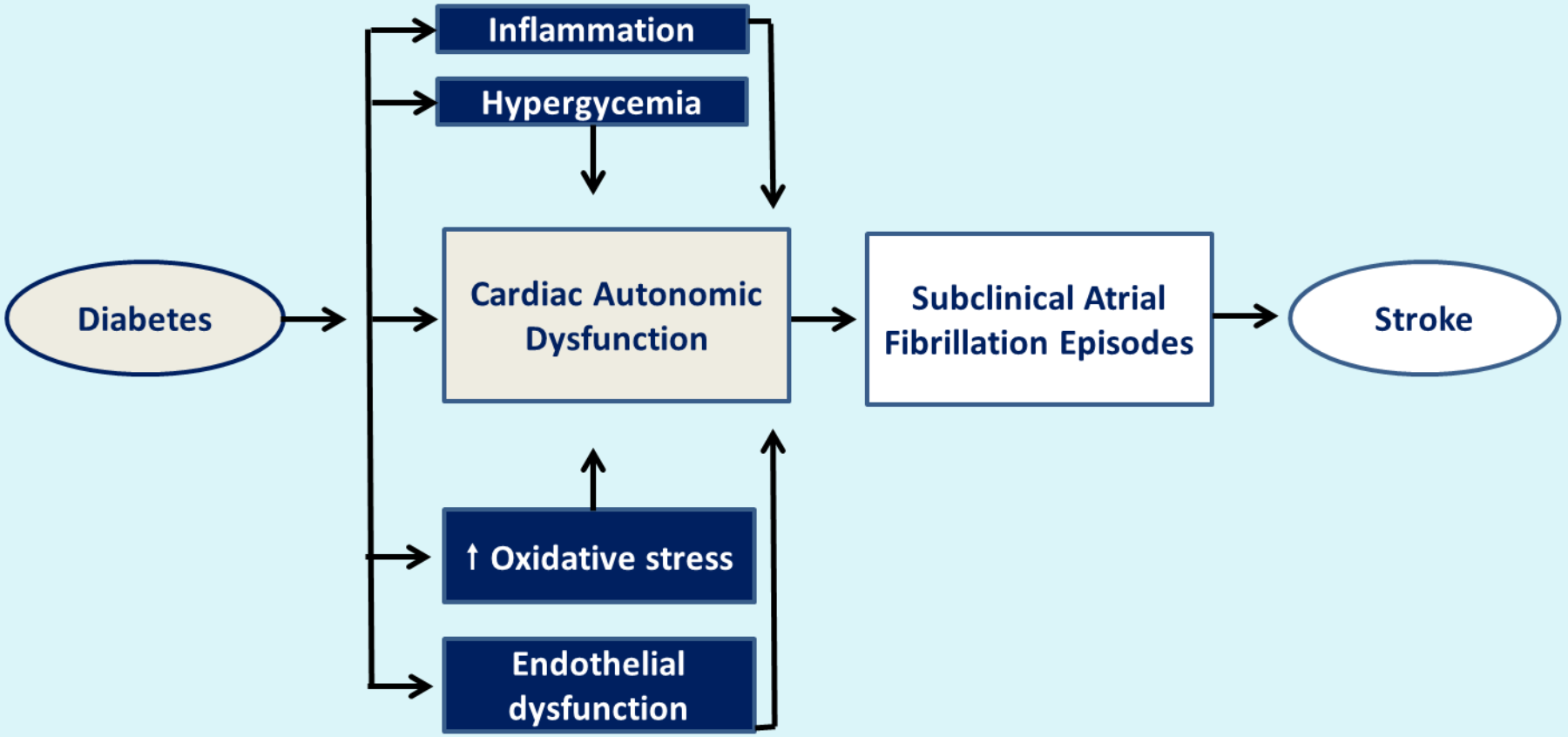
LF/HF ratio >6= ↑ sympathetic tone



Diabetes Care submitted data

Diabetes and the developement of the cryptogenic stroke

Primary methabolic disturbance → Resulting risk factor → Pathology → Critical event



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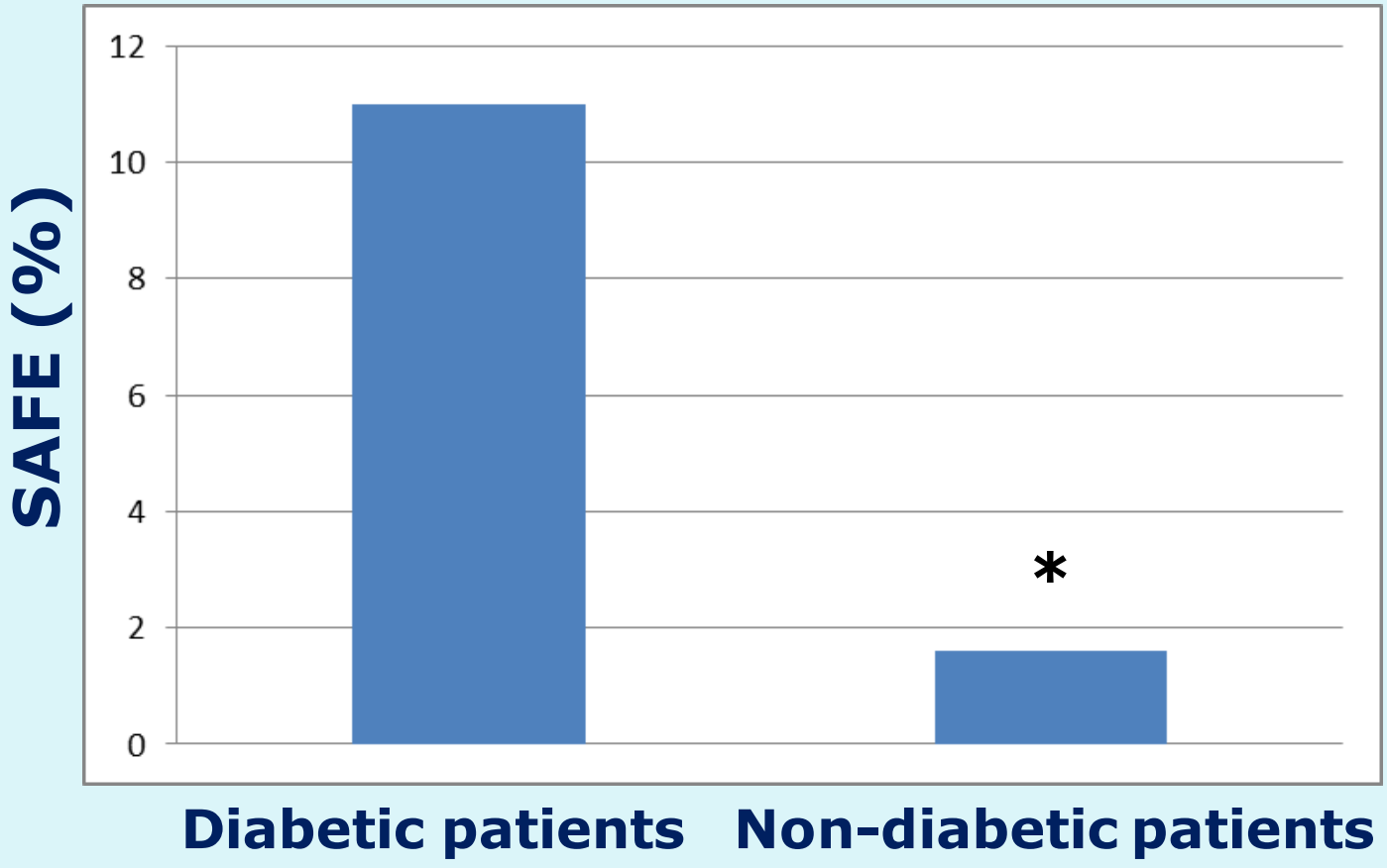
Journal of the American College of Cardiology

SAFE burden in diabetic and non diabetic patients



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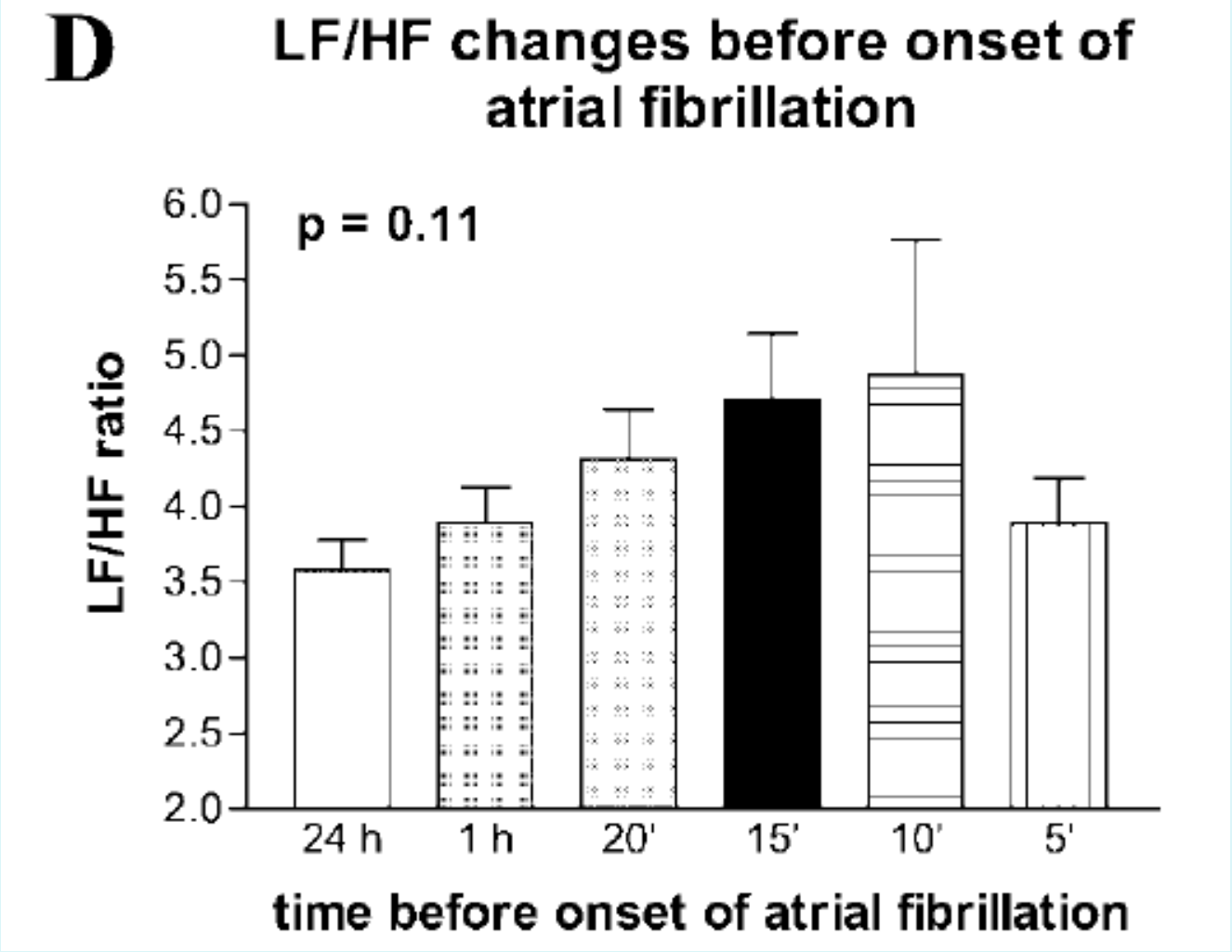
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Circulation. 2002;105:2753-2759

Autonomic Tone Variations Before the Onset of Paroxysmal Atrial Fibrillation

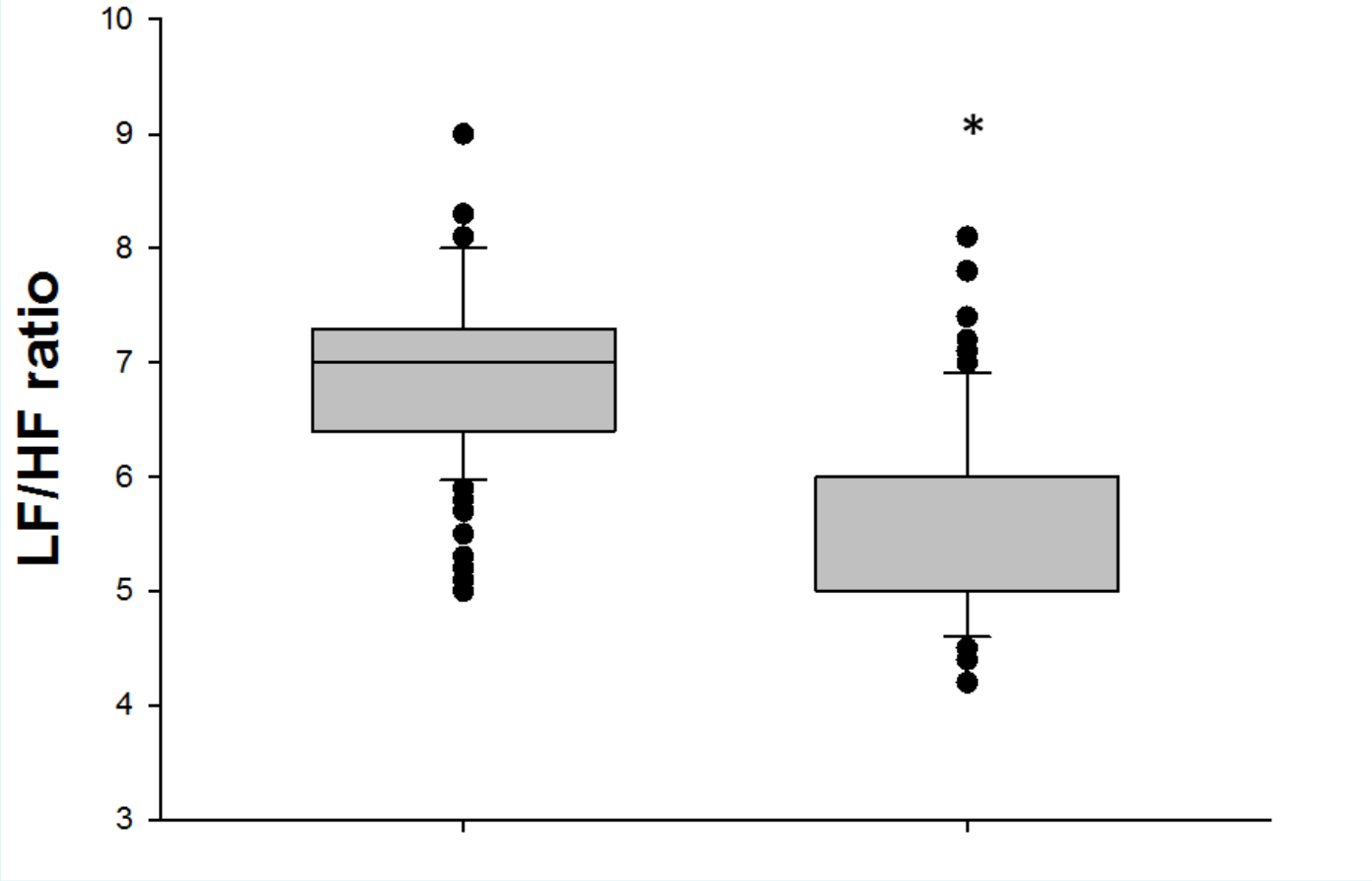
Marco Bettoni and Marc Zimmermann

Conclusions—The occurrence of PAF greatly depends on variations of the autonomic tone, with a primary increase in adrenergic tone followed by an abrupt shift toward vagal predominance. **(*Circulation*. 2002;105:2753-2759.)**



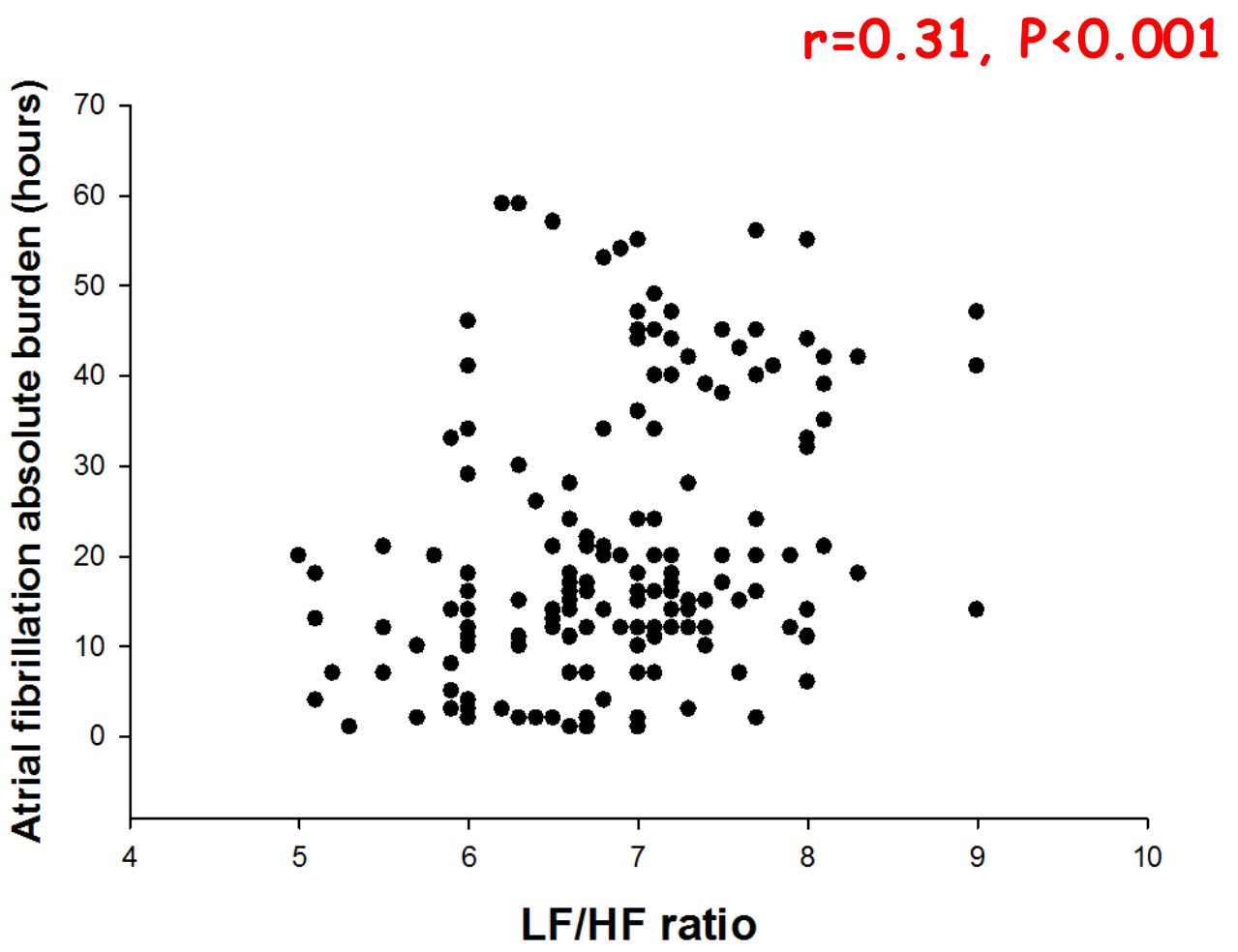
Autonomic dysfunction is associated with brief episodes of atrial fibrillation in type 2 diabetes?

Figure 1. Low-frequency/high-frequency (LF/HF ratio) in SAFE and no-SAFE patients. (Boxplot, a plot type that displays the median, 25th, and 75th percentiles, range, and extreme values) *P<0.05 compared with SAFE patients.



Diabetes Care submitted data

Linear regression between atrial fibrillation burden and LF/HF ratio.



Diabetes Care submitted data

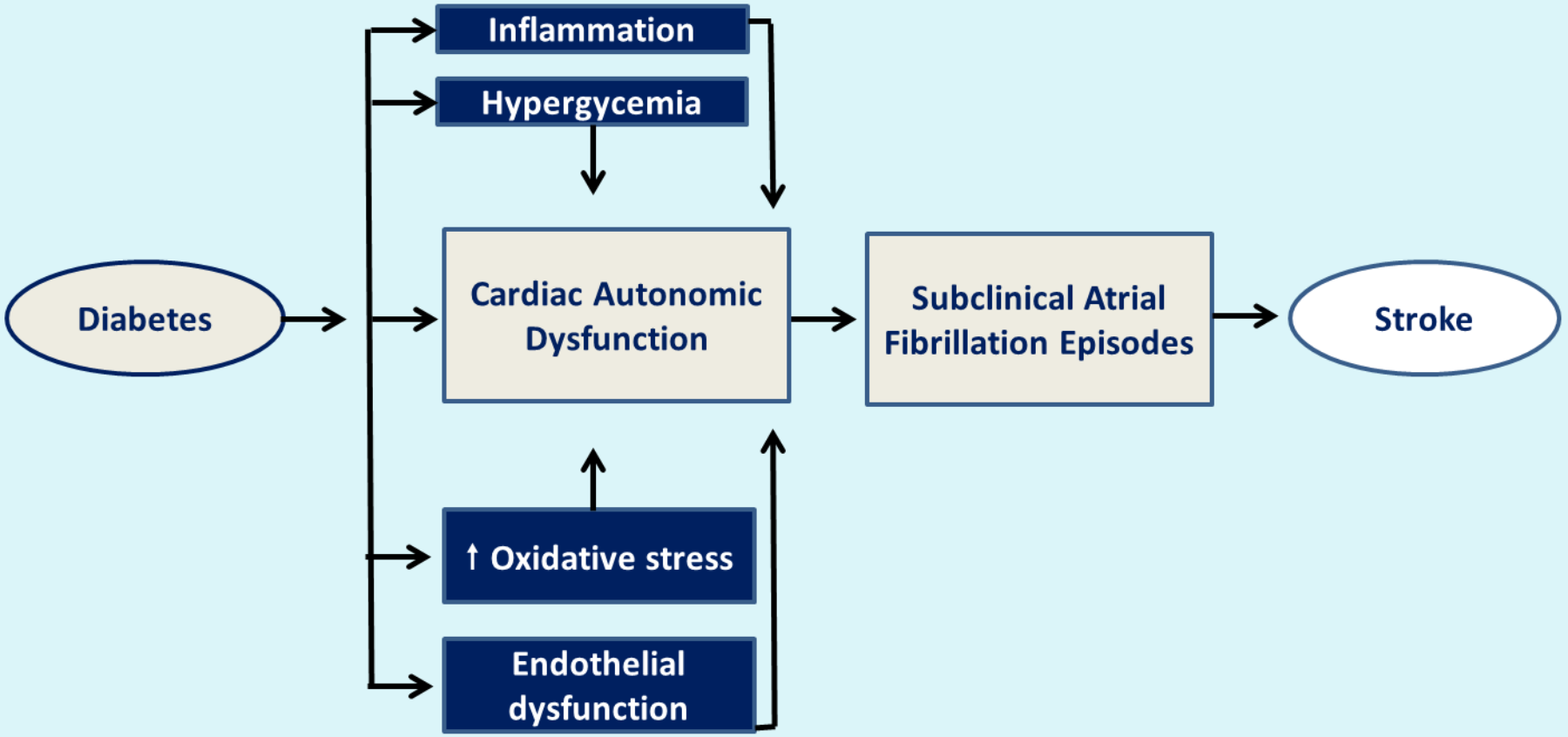
Multiple Logistic Regression for silent atrial fibrillation episodes

Independent Variable	Odds Ratio	5% Conf.	95% Conf.	P
Age	0.992	0.947	1.040	0.749
LF/HF ratio	**7.248**	**5.145**	**10.209**	**<0.001**
IVS	0.856	0.687	1.067	0.166
Left atrial Diameter	4.039	2.121	8.063	<0.001
Diabetes duration	0.951	0.875	1.032	0.227
HbA1c	1.115	0.744	1.671	0.598
Fasting glucose	1.007	0.994	1.020	0.294
Postprandial glucose	1.003	0.992	1.015	0.581
CIMT	0.266	0.0344	2.053	0.204
Body mass index	0.916	0.793	1.058	0.232
Systolic BP	3.442	1.831	6.348	<0.001
Diastolic BP	1.020	0.977	1.065	0.370
Heart rate	0.986	0.953	1.021	0.427
Total cholesterol	1.006	0.994	1.018	0.360
Triglycerides	0.981	0.967	1.995	0.541
HDL-cholesterol	0.688	0.486	0.975	<0.01

Diabetes Care submitted data

Diabetes and the developement of the cryptogenic stroke

Primary methabolic disturbance → Resulting risk factor → Pathology → Critical event

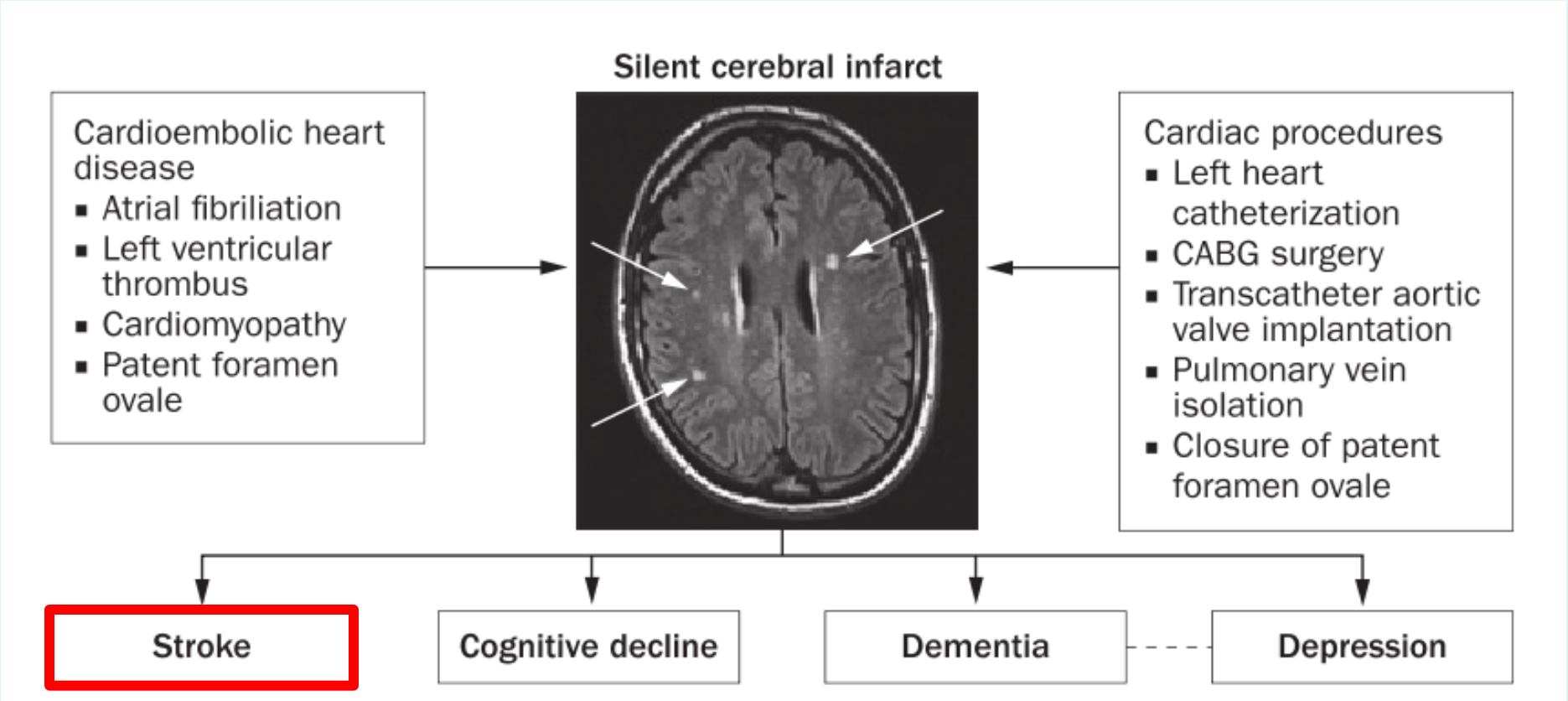


Silent brain infarcts: a systematic review

Sarah E Vermeer, William T Longstreth Jr, Peter J Koudstaal

Lancet Neurol 2007; 6: 611–19

SCI are described as parenchymal lesions that have MRI characteristics (≥3 mm) of a previous infartc event, but are not associated with clinical signs or symptoms of stroke or TIA.



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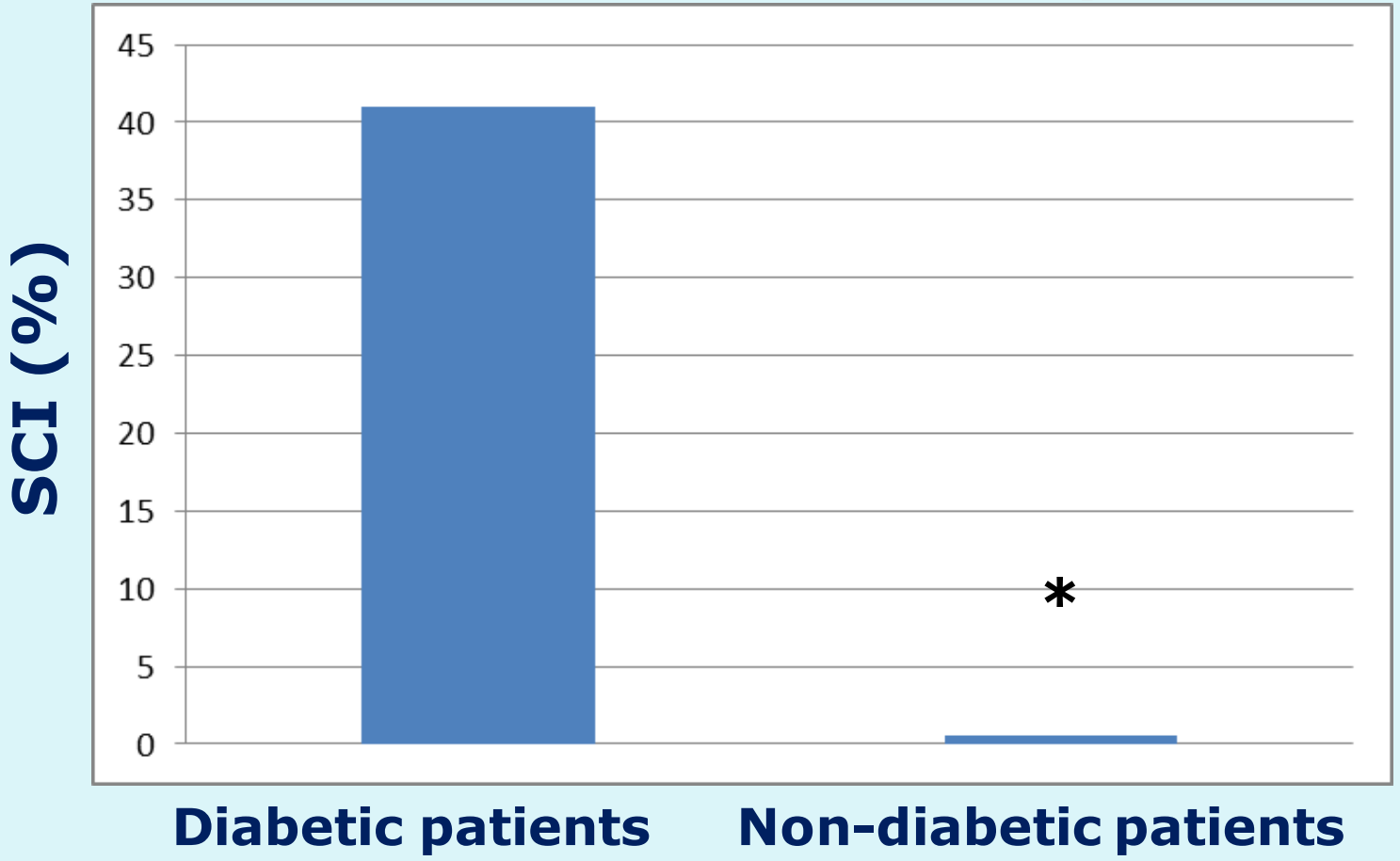
Journal of the American College of Cardiology

Silent cerebral infarct (SCI) burden in diabetic and non diabetic patients



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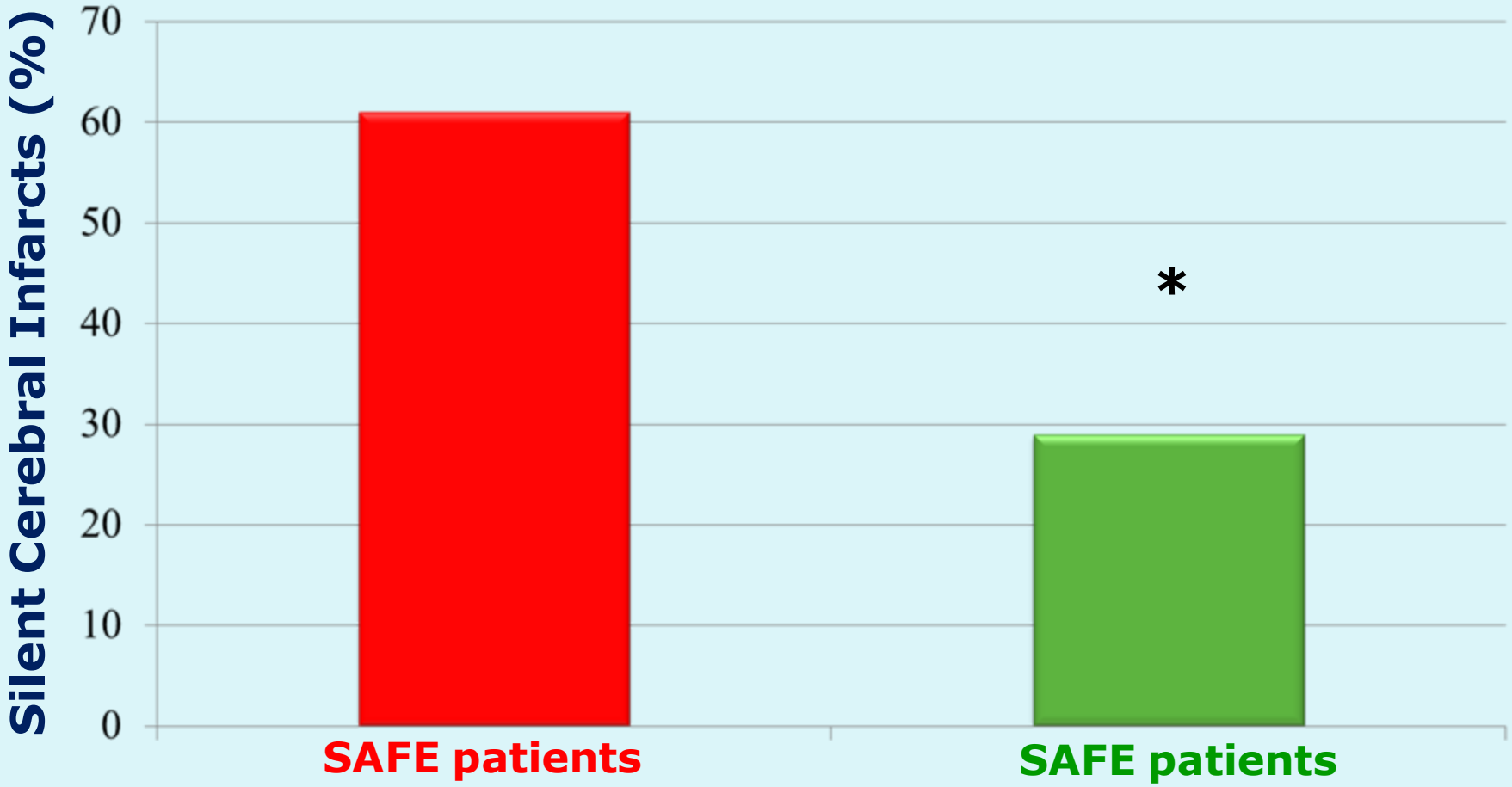
Silent Cerebral Infarcts



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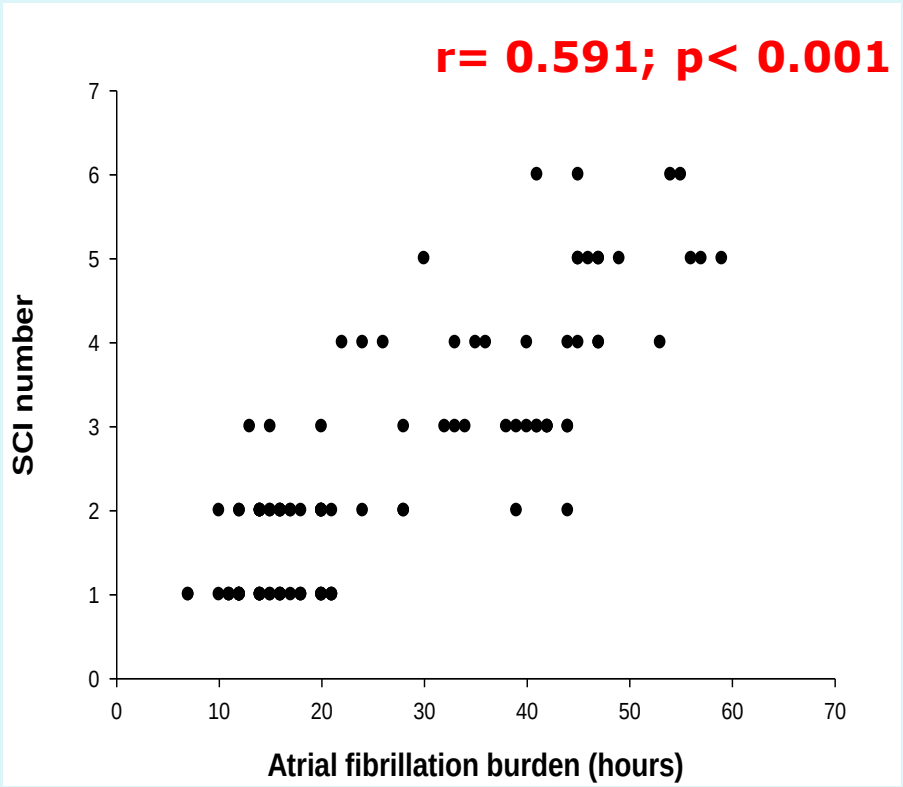
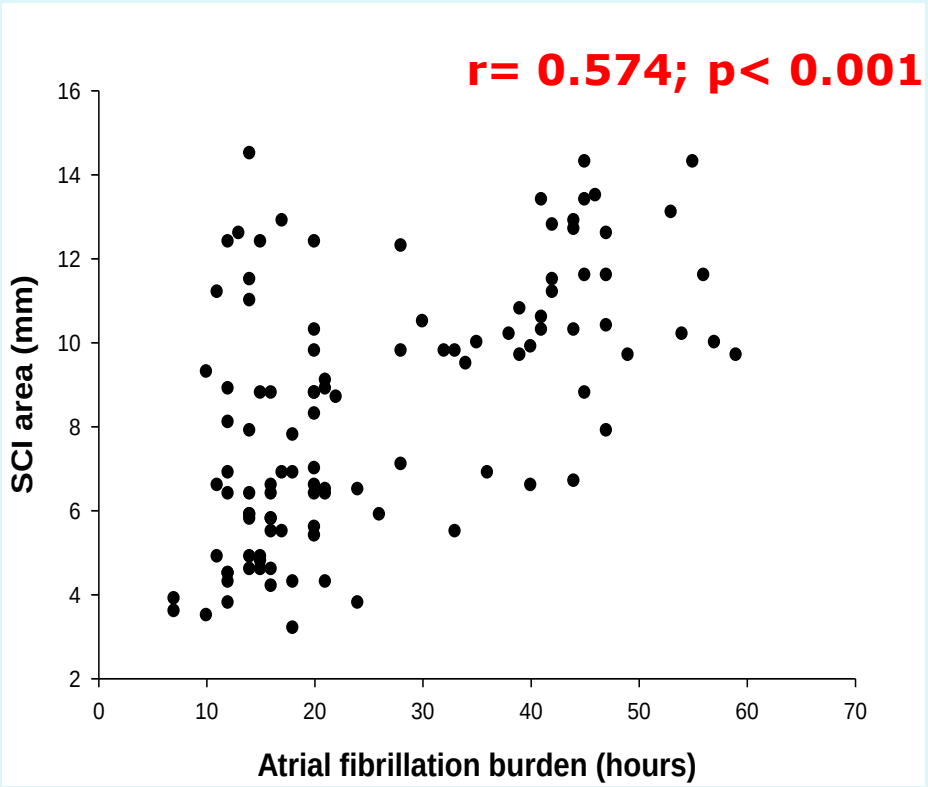
Linear Regression Between SCI Lesions and Episodes of AF





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August 6, 2013:525–30

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Table 2 Multiple Logistic Regression Analysis for Silent Cerebral Infarcts

Independent Variable	Odds Ratio	5% Lower Confidence Interval	95% Upper Confidence Interval	p Value
Age	1.005	0.965	1.047	0.793
Silent episodes of atrial fibrillation	4.441	2.418	8.157	0.001
Interventricular septum	0.886	0.736	1.068	0.204
Left atrial diameter	2.667	1.476	4.821	0.024
Duration of diabetes	1.075	1.002	1.154	0.044
Hemoglobin A_{1c}	0.688	0.468	1.355	0.134
Fasting glucose	0.889	0.699	1.025	0.158
Post-prandial glucose	1.010	0.999	1.022	0.203
Carotid intima-media thickness	0.273	0.0528	1.411	0.121
Body mass index	0.743	0.657	1.841	0.168
Systolic blood pressure	1.030	1.010	1.050	0.002
Diastolic blood pressure	0.975	0.939	1.012	0.179
Heart rate	0.973	0.944	1.002	0.069
Cholesterol	0.997	0.987	1.008	0.616
Triglycerides	0.991	0.979	1.004	0.164
High-density lipoprotein cholesterol	0.945	0.877	1.017	0.130

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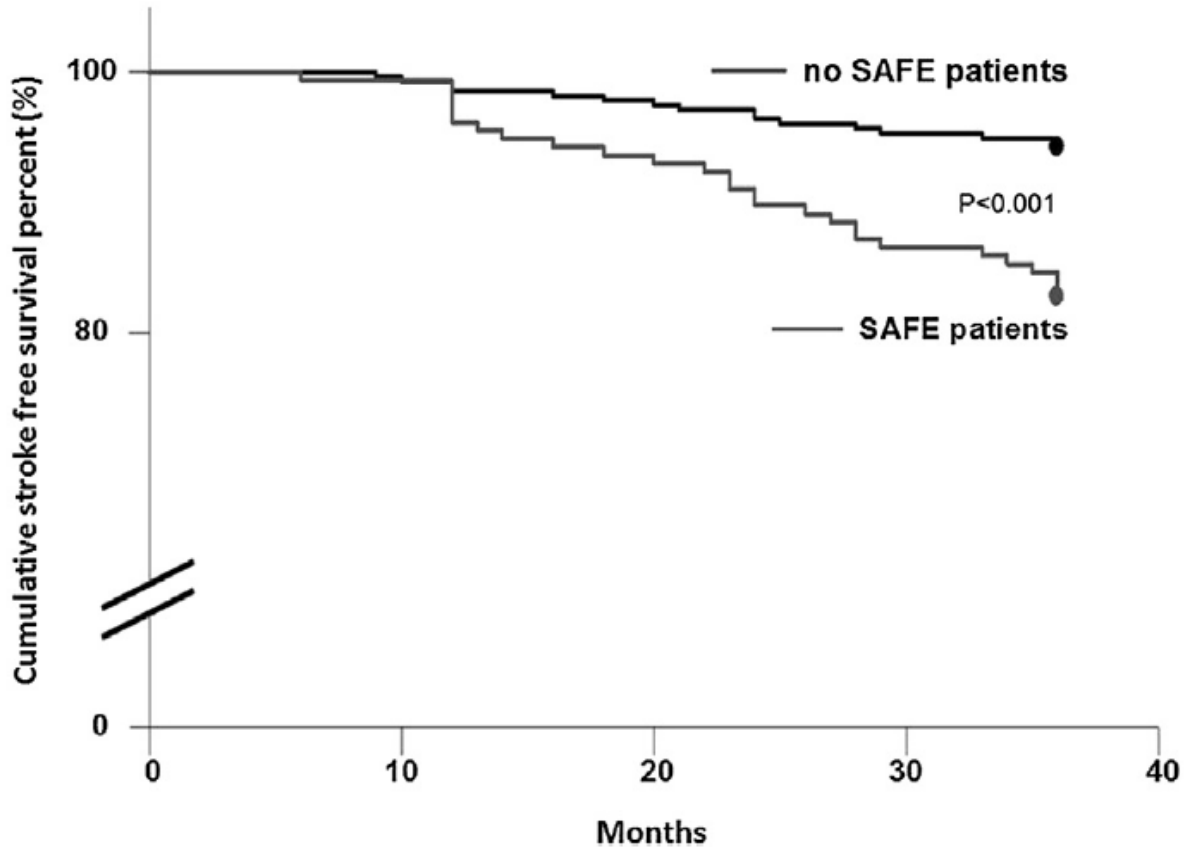

Figure 2 **Kaplan-Meier Curves for Adverse Events**

Kaplan-Meier curves for the unadjusted rate of occurrence of stroke in patients with or without silent episodes of atrial fibrillation.

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Journal of the American College of Cardiology

Multiple Logistic Regression Analysis for ischemic stroke

Independent Variable	Odds Ratio	5% Conf. Lower	95% Conf. Upper	P
SAFE	4.641	2.718	9.157	0.001
SCI	3.120	1.342	7.122	0.005
Systolic BP	1.730	1.020	2.920	0.011

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JACC Vol. 62, No. 6, 2013
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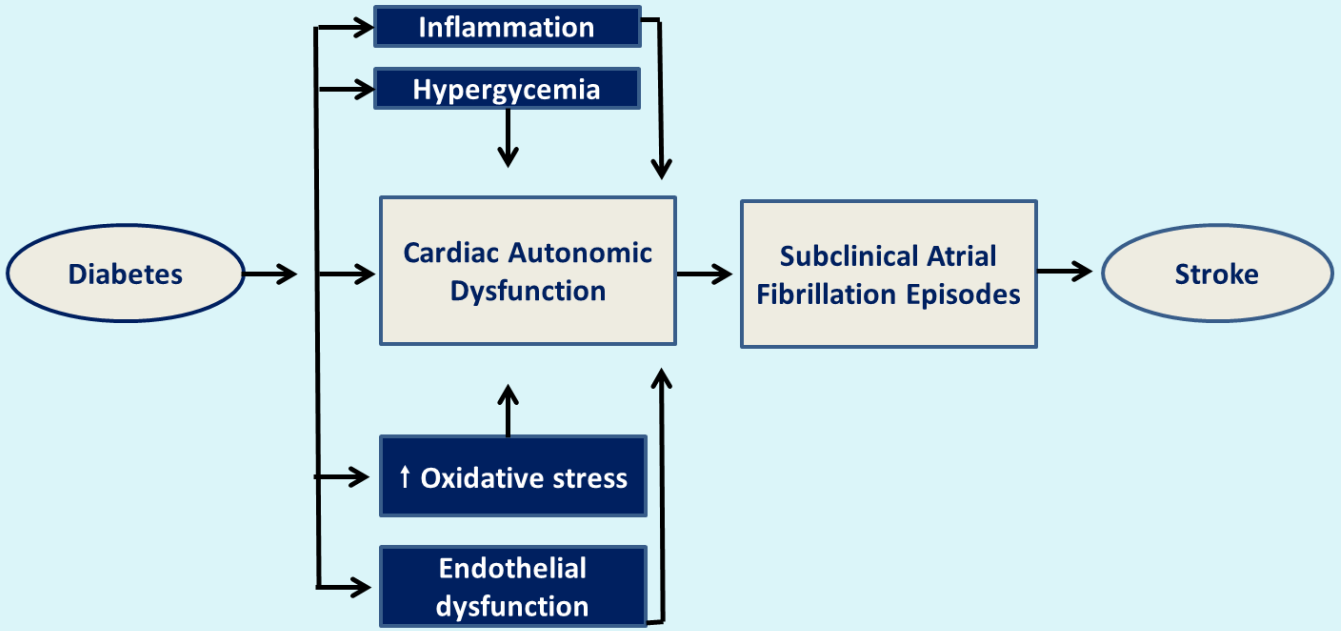
Brief Episodes of Silent Atrial Fibrillation Predict Clinical Vascular Brain Disease in Type 2 Diabetic Patients

Raffaele Marfella, MD, PhD,* Ferdinando Carlo Sasso, MD, PhD,† Mario Siniscalchi, MD, PhD,‡ Mario Cirillo, MD,§ Pasquale Paolisso,* Celestino Sardu, MD,* Michelangela Barbieri, MD, PhD,* Maria Rosaria Rizzo, MD, PhD,* Ciro Mauro, MD,† Giuseppe Paolisso, MD, PhD*

Naples, Italy

Diabetes and the developement of the cryptogenic stroke

Primary methabolic disturbance → Resulting risk factor → Pathology → Critical event



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Primary prevention

The identification of "brief episodes of AF",
by Holter monitoring,
may have clinical relevance in
prevention for stroke
in type 2 diabetic patients

Type 2 Diabetes →

48h quarterly

Secondary prevention

The identification of "brief episodes of AF",
by continuous cardiac monitoring after Stroke,
may have clinical relevance in
secondary prevention for stroke
in type 2 diabetic patients

Newly Diagnosed Atrial Fibrillation after Acute Ischemic Stroke and Transient Ischemic Attack: Importance of Immediate and Prolonged Continuous Cardiac Monitoring

Luciano A. Sposato, MD, MBA,*† Francisco R. Klein, MD,* Agustín Jáuregui, MD,* Marisol Ferrúa, MD,* Pablo Klin, MD,‡ Rafael Zamora, MD,§ Patricia M. Riccio, MD,* and Alejandro Rabinstein, MD¶

Journal of Stroke and Cerebrovascular Diseases, Vol. 21, No. 3 (April), 2012: pp 210-216

Figure 2. *Time elapsed between admission and NDAF.*

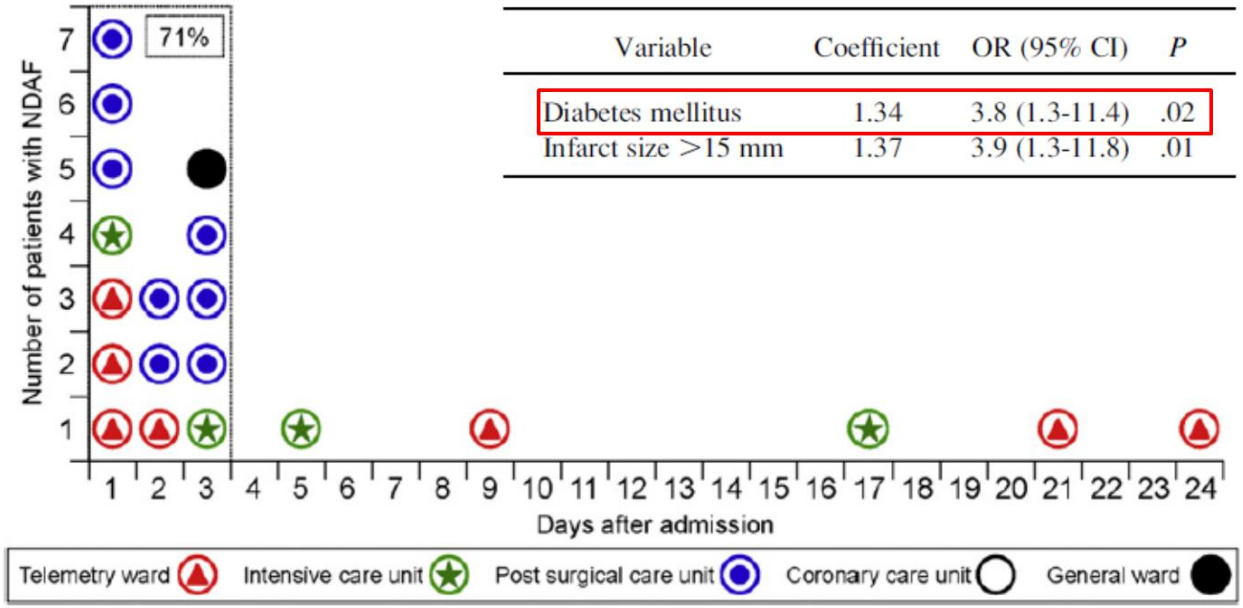

Table 3. *Determinants of NDAF in the logistic regression model*

Variable	Coefficient	OR (95% CI)	*P*
Diabetes mellitus	1.34	3.8 (1.3-11.4)	.02
Infarct size >15 mm	1.37	3.9 (1.3-11.8)	.01

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EDITORIAL COMMENT

Preserve the Brain

Primary Goal in the Therapy of Atrial Fibrillation*

Eric N. Prystowsky, MD, Benzy J. Padanilam, MD

Indianapolis, Indiana

We must do more:

- To identify patients with silent AF and a significant stroke risk, for example, the elderly or those with hypertension or diabetes;
- To evaluate new strategies to fulfill the first commandment of therapy for patients with AF

preserve the brain.

Circulation
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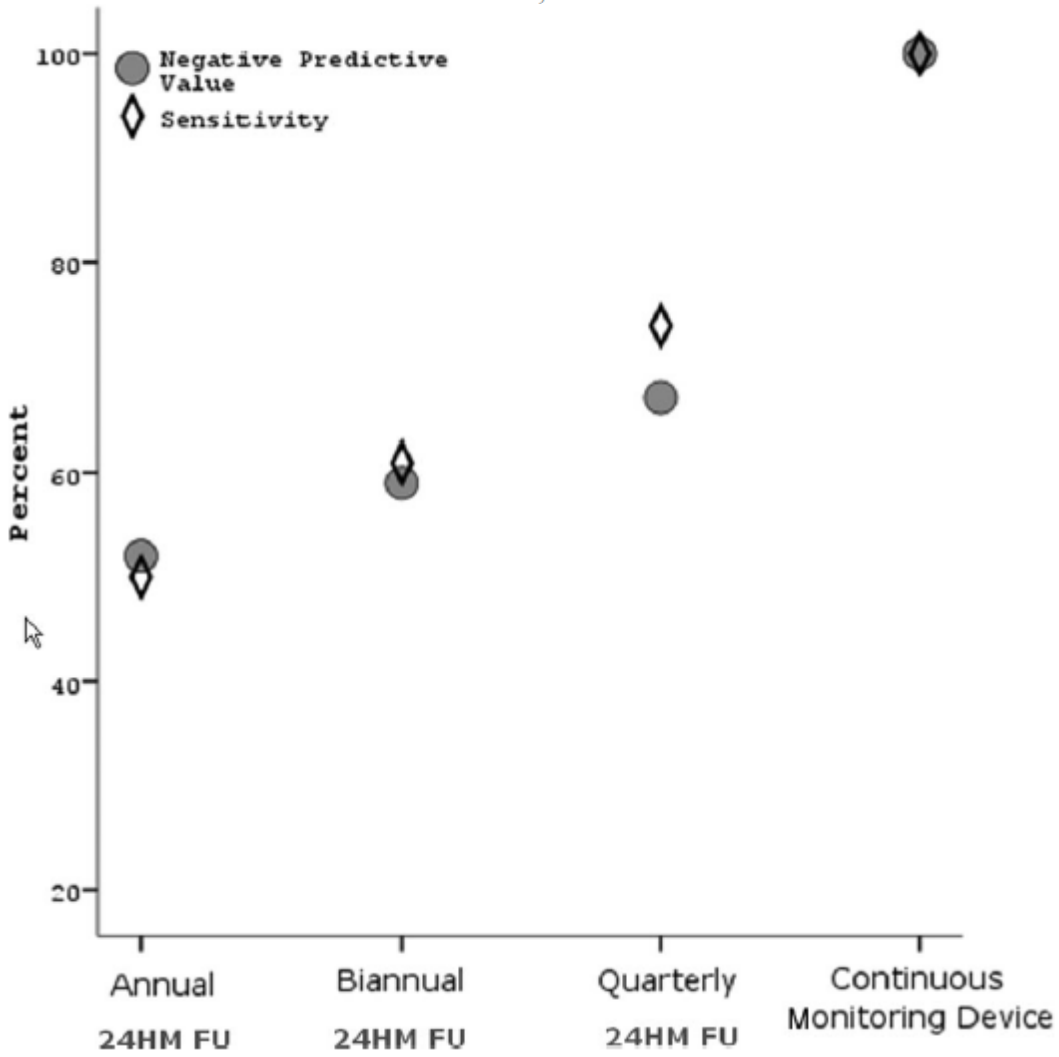
Twenty-Four–Hour Holter Monitor Follow-Up Does Not Provide Accurate Heart Rhythm Status After Surgical Atrial Fibrillation Ablation Therapy : Up to 12 Months Experience With a Novel Permanently Implantable Heart Rhythm Monitor Device

Thorsten Hanke, Efstratios I. Charitos, Ulrich Stierle, Antje Karluss, Ernst Kraatz, Bernhard Graf, Axel Hagemann, Martin Misfeld and Hans H. Sievers

Circulation. 2009;120:S177-S184